ASSESSMENT REPORT ON

ETHYLBENZENE

FOR DEVELOPING AMBIENT AIR QUALITY OBJECTIVES

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FOR DEVELOPING AN AMBIENT AIR QUALITY OBJECTIVES

Prepared by
Cantox Environmental Inc.

IN CONJUNCTION WITH
RWDI West Inc.

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Any comments, questions, or suggestions regarding the content of this document may be directed to:

Science and Standards Branch
Alberta Environment
4th Floor, Oxbridge Place
9820 – 106th Street
Edmonton, Alberta T5K 2J6
Fax: (780) 422-4192

Additional copies of this document may be obtained by contacting:

Information Centre
Alberta Environment
Main Floor, Oxbridge Place
9820 – 106th Street
Edmonton, Alberta T5K 2J6
Phone: (780) 427-2700
Fax: (780) 422-4086
Email: env.infocent@gov.ab.ca

FOREWORD

Alberta Environment maintains Ambient Air Quality Objectives[1] to support air quality management in Alberta. Alberta Environment currently has ambient objectives for more than thirty substances and five related parameters. These objectives are periodically updated and new objectives are developed as required.

With the assistance of the Clean Air Strategic Alliance, a multi-stakeholder workshop was held in October 2000 to set Alberta's priorities for the next three years. Based on those recommendations and the internally identified priority items by Alberta Environment, a three-year work plan ending March 31, 2004 was developed to review four existing objectives, create three new objectives for three families of substances, and adopt six new objectives from other jurisdictions.

In order to develop a new three-year work plan, a multi-stakeholder workshop was held in October 2004. This study was commissioned in preparation for the workshop to provide background information on alternative, science based, and cost effective methods for setting priorities.

This document is one of a series of documents that presents the scientific assessment for these adopted substances.

Long Fu, Ph. D.
Project Manager
Science and Standards Branch

[1] **NOTE**: The *Environmental Protection and Enhancement Act*, Part 1, Section 14(1) refers to "ambient environmental quality objectives" and uses the term "guidelines" in Section 14(4) to refer to "procedures, practices and methods for monitoring, analysis and predictive assessment." For consistency with the *Act*, the historical term "ambient air quality guidelines" is being replaced by the term "ambient air quality objectives." This document was prepared as the change in usage was taking place. Consequently any occurrences of "air quality guideline" in an Alberta context should be read as "air quality objective."

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Mr. Rob Willis, B.Sc., M.E.S., CCEP
Cantox Environmental Inc.
Halifax, Nova Scotia

Dr. Gord Brown, PhD, QEP
Cantox Environmental Inc.
Calgary, Alberta

Mr. Bart Koppe, B.Sc., P.B.D. (Environmental Toxicology), P.Biol.
Cantox Environmental Inc.
Calgary, Alberta

Ms. Christine McFarland, B.Sc.
Cantox Environmental Inc.
Calgary, Alberta

Ms. Lisa Marshall, B.Sc., P.B.D., M.E.S.
Cantox Environmental Inc.
Halifax, Nova Scotia

Mr. Sachin Bhardwaj
Technical Coordinator
RWDI West Inc.
Calgary, Alberta

Mr. Sanjay Prasad, B.Sc., EPI
Air Quality Technical Coordinator
RWDI West Inc.
Calgary, Alberta

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ACRONYMS, ABBREVIATIONS, AND DEFINITIONS

AAL	Allowable Ambient Level (Massachusetts) or Acceptable Ambient Level (North Carolina)
AAQC	Ambient Air Quality Criteria
AAS	Ambient Air Standard (Louisiana)
ACGIH	American Conference of Governmental Industrial Hygienists
AGC	Annual Guideline Concentration (New York State)
ANR	Vermont Agency of Natural Resources (Vermont)
ASIL	Acceptable Source Impact Level (Washington Department of Ecology)
ATC	Allowable Threshold Concentration – continuous exposure (daily lifetime) (Massachusetts DEP)
ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
CalEPA	California Environmental Protection Agency
CAPCOA	California Air Pollution Control Officers Association
CAS	Chemical Abstracts Service
CCME	Canadian Council of Ministers of the Environment
CEIL	Ceiling Value
CEPA	Canadian Environmental Protection Act
DEC	Department of Environmental Conservation (*e.g.*, New York)
DENR	Department of Environment and Natural Resources (*e.g.*, North Carolina)
DEP	Department of Environmental Protection (*e.g.*, Massachusetts, New Jersey)
DES	Department of Environmental Services (*e.g.*, New Hampshire)
DEQ	Department of Environmental Quality (*e.g.*, Michigan, Louisiana, Oklahoma
DOE	Department of Environment or Department of Ecology (*e.g.*, Washington)
ENEV	Estimated No-Effects Value
EPA	Environmental Protection Agency (*e.g.*, Ohio)
ESL	Effects Screening Level
GLC	Ground Level Concentration
GV	Guideline Value
HAAS	Hazardous Ambient Air Standard
HEAST	Health Effects Assessment Summary Tables
HEC	Human Equivalent Concentration
HRV	Health Risk Value
IARC	International Agency for Research on Cancer
IHRV	Inhalation Risk Value
IRIS	Integrated Risk Information System
IRSL	Initial Risk Screening Level
ITSL	Interim Threshold Screening Level
LC50	Median Lethal Concentration
LD50	Median Lethal Dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEC	Lowest-Observed-Effect Concentration
LOEL	Lowest-Observed-Effect Level
MAAC	Maximum Acceptable Ambient Air Concentration

MAAQC	Maximum Annual Air Quality Criteria
MAC	Maximum Acceptable Concentration
MACT	Maximum Achievable Control Technology
MAGLC	Maximum Acceptable Ground-Level Concentration
MDH	Minnesota Department of Health
MHRV	Multimedia Health Risk Value
MIC	Maximum Immission Concentration (Netherlands)
MPR	Maximum Permissible Risk Level
MRL	Minimal Risk Level
MTLC	Maximum Tolerable Level Concentration
NAAQO	National Ambient Air Quality Objective
NIEHS	National Institute of Environmental Health Sciences (USA)
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-Observed-Adverse-Effect Level
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
NPRI	National Pollutant Release Inventory
NRCC	Natural Resource Conservation Commission
NTP	National Toxicology Program (USA)
OEHHA	Office of Environmental Health Hazard Assessment (California EPA)
OEL	Occupational Exposure Limit
OMOE	Ontario Ministry of Environment
OSHA	Occupational Safety and Health Association
PEL	Permissible Exposure Limit
PM	Particulate Matter
POI	Point of Impingement
PSL	Priority Substance List
PSL1	First Priority Substances List (Canada)
PSL2	Second Priority Substances List (Canada)
RD50	Median Respiration Rate Decrease
REL	Either Reference Exposure Limit as used by the California EPA or Recommended Exposure Limit used by both NIOSH and ATSDR
RfC	Reference Concentration
RfD	Reference Dose
RIVM	Netherlands Research for Man and Environment
RM	Risk Management
RTECS	Registry of Toxic Effects of Chemical Substances
SGC	Short-term Guideline Concentration
SRSL	Secondary Risk Screening Level
STEL	Short-term Exposure Limit
T-BACT	Best Available Control Technology for Toxics
TC	Tolerable Concentration
TCA	Tolerable Air Concentration
TC01	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 1% increase in incidence or mortality due to tumours

TC05	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 5% increase in incidence or mortality due to tumours
TD05	Tumorigenic Dose - the total intake of a contaminant generally associated with a 5% increase in incidence or mortality due to tumours
TEL	Threshold Effects Exposure Level
TLV	Threshold Limit Value
TNRCC	Texas Natural Resource Commission
TWA	Time-Weighted-Average
U.S. EPA	United States Environmental Protection Agency
WHO	World Health Organization

ppm	parts per million
ppb	parts per billion
mg	a milligram, one thousandth of a gram
µg	a microgram, one millionth of a gram
ng	a nanogram, one billionth of a gram

SUMMARY

Ethylbenzene is a clear, colourless, volatile liquid under standard conditions. It is a flammable liquid and is combustible at room temperature and standard atmospheric pressure. Ethylbenzene is manufactured primarily *via* the alkylation of benzene with ethylene in liquid-phase slurry reactors promoted with aluminum trichloride, or *via* vapour-phase reaction of benzene with dilute ethylene-containing feedstock with boron trifluoride catalyst supported on alumina. Ethylbenzene is primarily used as a precursor in the production of styrene and cellulose acetate, but is found in a large number of industrial, commercial and consumer products. Ethylbenzene is a naturally occurring component of crude oil. It is formed during combustion of organic materials; thus, forest, grass and other biomass fires will release ethylbenzene to the atmosphere.

The majority of ethylbenzene releases to the environment are to the atmosphere. Ethylbenzene may be released to air during various manufacturing processes that use this substance as well as its storage, handling, transportation and disposal. Ethylbenzene is emitted to air in virtually all combustion processes, including all point and mobile combustion sources that utilize fossil fuels. In indoor environments, major sources of ethylbenzene are consumer products and cigarette smoke. Ethylbenzene is therefore ubiquitous in outdoor and indoor urban and rural air.

Given its high vapour pressure, ethylbenzene is expected to exist solely as a vapour in the ambient atmosphere. It is degraded in the atmosphere primarily *via* reaction with photochemically-produced hydroxyl radicals. The photooxidation half-life for this reaction in air is reported to vary between 0.5 hours to two days. This results in a short atmospheric lifetime and also limits the atmospheric transport of this substance.

The major sector in Alberta that releases ethylbenzene to air is the oil and gas sector, with the top contributors including oil sands operations, petroleum refineries, petrochemical plants and gas plants. For the majority of these facilities, fugitive emissions comprise the most significant portion of ethylbenzene emissions to air, although stack emissions and releases during storage and handling can also be significant at some facilities.

Ethylbenzene is rapidly and efficiently absorbed *via* the inhalation exposure route and is efficiently distributed throughout the body. The metabolism of ethylbenzene is complex. In general, ethylbenzene is metabolized mainly through hydroxylation and then through conjugation reactions from which numerous metabolites have been isolated. Urinary excretion has been shown to be the primary route of elimination of ethylbenzene metabolites in both humans and experimental animals following inhalation exposure.

In humans, the symptoms of acute ethylbenzene intoxication following inhalation exposure include: respiratory tract and ocular irritation, lacrimation (tearing), chest constriction, a burning sensation, dizziness, vertigo and minor hematological changes. Symptoms of acute ethylbenzene toxicity in experimental animals are similar to those observed in humans in that eye and respiratory tract irritation is frequently reported, but acute toxicity in animals is also manifested by neurological and neurobehavioral effects, hearing impairment, altered liver and kidney enzyme levels and increased liver weights.

The carcinogenicity evidence for ethylbenzene is equivocal. While there is evidence of carcinogenic effects in rats and mice, it appears that the observed renal tumour types cannot be extrapolated to humans. The weight of available evidence from genotoxicity and mutagenicity studies strongly suggests that ethylbenzene is not mutagenic in most test systems. No association has been found between the occurrence of cancer in humans and occupational exposure to ethylbenzene.

The review of the physical chemical properties (Section 2.0) and toxicology (Section 4.0) of ethylbenzene indicates several key benchmark air concentrations that should be considered in establishing an ambient air quality guideline. Odour thresholds for ethylbenzene are highly variable and have been reported to range from as low as 0.4 mg/m^3 to as high as 78.3 mg/m^3 (WHO, 1996; Verschueren, 1983; van Gemert, 1999; Amoore and Hautala, 1983; Cometto-Muniz and Cain, 1995).

A number of acute human and animal studies have demonstrated various adverse effects at concentrations above 300 ppm (1,305 mg/m^3). At air concentrations below 100 ppm (435 mg/m^3) there appear to be no adverse effects, including a lack of irritation effects. All current occupational exposure limits for ethylbenzene derived by ACGIH, NIOSH and OSHA are based on human studies in which irritant effects were demonstrated at air concentrations above 100 ppm (435 mg/m^3).

Subchronic and chronic inhalation studies with ethylbenzene in experimental animals have demonstrated a variety of adverse effects. NTP (1992) reported a LOAEL of 1,000 ppm (4,350 mg/m^3) for organ weight changes. A NOAEL of 75 ppm (326 mg/m^3) was suggested by OEHHA (2003) from the NTP (1999) study based on a variety of non-neoplastic effects in rats and mice. The U.S. EPA (1991) identified NOAEL (HEC) values of 606 mg/m^3 in mice and rats, and 1,249 mg/m^3 in rabbits, from the Cragg *et al.* (1989) study. From the study by Elovaara *et al.* (1985), the U.S. EPA (1991) identified a NOAEL (HEC) of 465 mg/m^3.

The available human epidemiology studies are inconclusive and suffer from a number of methodological and reporting limitations, and are confounded by concurrent exposures to other chemicals.

No human studies were identified that investigated the reproductive or developmental effects of ethylbenzene following inhalation exposure. A few animal studies have investigated the reproductive and/or developmental toxicology of ethylbenzene by the inhalation route. From the study by Ungvary and Tatrai (1985), the U.S. EPA (1991) identified a LOAEL of 2,400 mg/m^3 for extra ribs in the absence of demonstrable maternal toxicity (although confidence in this particular study is low due to a number of methodological and reporting deficiencies). From the study by Andrew *et al.* (1981), the U.S. EPA (1991) identified a developmental NOAEL of 100 ppm in rabbits, which equates to a NOAEL (HEC) of 434 mg/m^3. From this same study, a LOAEL of 1,000 ppm (4,350 mg/m^3) was identified based on increased absolute and relative liver, kidney and spleen weights in pregnant rats, as well as minor skeletal variants in F1 offspring.

For those agencies with guidelines, the basis is either the U.S. EPA RfC of 1.0 mg/m^3, the studies by Andrew *et al.* (1981) and Hardin *et al.* (1981), or the ACGIH TLV-TWA or STEL values of 100 ppm (435 mg/m^3) or 125 ppm (544 mg/m^3), respectively (adjusted with various modifying and uncertainty factors). The TNRCC criteria differ from the other jurisdictions reviewed in that they are based upon odour effects of ethylbenzene, rather than health effects data. All available air quality guideline values appear to be adequately protective of human health. In addition, given the available data on the environmental fate, transport and effects of ethylbenzene, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns. The photooxidation of ethylbenzene could produce such products as peroxyacetyl nitrate, ethylphenol, benzaldehyde, acetophenone and ethylnitrobenzenes and may contribute to the formation of photochemical smog in the atmosphere (WHO, 1996). Peroxyacetyl nitrate (PAN) is a known irritant component of photochemical smog. However, ethylbenzene has a relatively low smog formation potential relative to other volatile hydrocarbons (ATSDR, 1999).

1.0 INTRODUCTION

Alberta Environment (AENV) establishes Ambient Air Quality Objectives under Section 14 of the Environmental Protection and Enhancement Act (EPEA). These guidelines are part of the Alberta Air Quality Management System (AENV, 2000a).

Ambient Air Quality Objectives (AAQO) provide the basis for determining whether or not ambient air quality is acceptable from a health perspective. For substances lacking Alberta objectives, the development of acceptable ambient air concentrations typically considers a number of factors, including physical-chemical properties, sources, effects on human and environmental health, air monitoring techniques and ambient air guidelines derived by other jurisdictions within Canada, the United States, various other countries, and multi-country organizations (*e.g.*, World Health Organization).

The main objective of this assessment report is to provide a review of scientific and technical information to assist in evaluating the basis and background for an Ambient Air Quality Objective for ethylbenzene. The following aspects were examined as part of this review:

- Physical and chemical properties
- Existing and potential natural and anthropogenic emissions sources in Alberta
- Effects on humans, animals and vegetation
- Monitoring techniques
- Ambient air guidelines in other Canadian jurisdictions, United States, European Union and Australia, and the basis for their development and use.

Key physical and chemical properties that govern the fate and behaviour of ethylbenzene in the environment are reviewed and presented in this assessment report. Existing and potential natural and anthropogenic sources of ethylbenzene air emissions in Alberta are also reviewed and presented in this report. This included information obtained from Environment Canada's National Pollutant Release Inventory (NPRI) and the National Air Pollution Surveillance Network (NAPS Network).

Scientific information regarding the toxic effects of ethylbenzene on humans and animals is reported in a number of sources, including toxicological and epidemiological studies published in peer-reviewed journals and detailed regulatory agency reviews such as those published by the International Agency for Research on Cancer (IARC), World Health Organization (WHO), U.S. Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Environmental Protection Agency's (U.S. EPA) Integrated Risk Information System (IRIS) and Toxicological Profiles, and Canadian Priority Substance List Reports under CEPA (1999). There is also a recent air quality guideline scientific support document for ethylbenzene from the Ontario Ministry of the Environment (OMOE, 2001). These sources provide valuable information for understanding the potential human and environmental health effects of ethylbenzene. Key information from these sources regarding the effects of airborne concentrations of ethylbenzene on humans, animals, plants and the environment is summarized in this report.

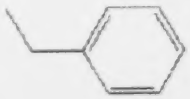
Air monitoring and measuring techniques for ethylbenzene in air are well documented in the peer-reviewed scientific and regulatory agency literature. Several widely used and accepted air monitoring reference methods exist for ethylbenzene that have been developed, tested and reported by such agencies as U.S. EPA, U.S. National Institute of Occupational Safety and Health (NIOSH) and U.S. Occupational Safety and Health Administration (OSHA). These methods and techniques are summarized in this report.

2.0 GENERAL SUBSTANCE INFORMATION

Ethylbenzene is a clear, colourless liquid under standard conditions (ATSDR, 1999; WHO, 1996; Verschueren, 1983; NTP, 2001; Lewis, 1997). The odour has been described as pungent (Clayton and Clayton, 1994), aromatic (Lewis, 1997; NTP, 2001) and gasoline-like (WHO, 1996). Ethylbenzene has low water solubility (ATSDR, 1999; WHO, 1996) but is soluble in ethanol and diethylether and miscible with most other organic solvents (Budavari, 1996; HSDB, 2003; Lewis, 1997; NTP, 2001; WHO, 1996). It is also soluble in sulphur dioxide, slightly soluble in chloroform, and insoluble in ammonia (NTP, 2001; WHO, 1996). Ethylbenzene reacts vigorously with nitric acid and oxidizing agents such as perchlorates, peroxides, permanganates, chlorates, nitrates, chlorine, bromine and fluorine (NTP, 2001; DHSS, 2002). Ethylbenzene is a flammable liquid and is combustible at room temperature and standard atmospheric pressure (ATSDR, 1999; NTP, 2001). Liquid ethylbenzene floats on water and may serve to spread a fire by floating back to the source of ignition (ATSDR, 1999). In addition, ethylbenzene vapours are heavier than air and may travel to the source of ignition and flash back (ATSDR, 1999). The combustion of ethylbenzene may produce irritants and toxic gases (ATSDR, 1999). Ethylbenzene exhibits the potential to accumulate static electricity (ATSDR, 1999).

Table 1 provides a list of common synonyms, trade names and identification numbers for ethylbenzene.

Table 1 Identification of Ethylbenzene

Property	Value
Formula	C_8H_{10}
Structure	
CAS Registry Number	100-41-4
RTECS Number	DA0700000
UN Number	UN 1175
Common Synonyms	EB Ethylbenzol Phenylethane
Trade names	EPA Hazardous Waste: F003 IMO 3.2 NCI-C56393 ACX No. X1003016-1 EEC No. 601-023-00-4

Ethylbenzene is manufactured *via* the alkylation of benzene with ethylene in liquid-phase slurry reactors promoted with aluminum trichloride or *via* vapour-phase reaction of benzene with dilute ethylene-containing feedstock with boron trifluoride catalyst supported on alumina (ATSDR, 1999; WHO, 1996). Ethylbenzene may also be produced by the dehydrogenation of naphthenes, preparation from acetophenone, catalytic cyclization and aromatization, separation from mixed xylenes *via* fractionation, reaction with ethyl magnesium bromide and chlorobenzene, extraction from coal oil and recovery from alkyl benzene processing (ATSDR, 1999; NTP, 2001). Commercial grades of ethylbenzene may contain small amounts of xylenes, cumene and toluene (HSDB, 2003).

In the United States in 1993, the estimated annual production for ethylbenzene was 5.3 million tonnes (WHO, 1996).

Ethylbenzene is primarily used as a precursor in the production of styrene and cellulose acetate (Lewis, 1997). It is also used as a precursor in the manufacture of diethylbenzene, acetophenone, ethyl anthraquinone, ethylbenzene sulfonic acids, propylene oxide and a-methylbenzyl alcohol (HSDB, 2003; NTP, 1999). Ethylbenzene is used as a solvent in paints, lacquers and resins and in the rubber manufacturing industry (HSDB, 2003; WHO, 1996). It is a component of crude oils, refined petroleum products and combustion products (WHO, 1996). Ethylbenzene is a major component (roughly 10 to 15%) of mixed xylenes that are widely used as solvents in agricultural and home insecticide sprays, household degreasers, paints, varnishes, adhesives and rust preventives, and it is used as an antiknock agent in aviation and motor fuels (NTP, 1999). Other consumer and commercial products containing ethylbenzene include liquid process photocopiers and plotters, carpet glue and fabric and leather treatments (ATSDR, 1999). Over 99% of the ethylbenzene produced in 1984 in the United States was used in styrene production, while the remainder was either exported or sold in solvent applications (HSDB, 2003).

The majority of ethylbenzene's environmental releases are to the atmosphere. Ethylbenzene may be released to air during various manufacturing processes that use this substance as well as its storage, handling, transportation and disposal. Ethylbenzene is also emitted to air in virtually all combustion processes, including all point and mobile combustion sources that utilize fossil fuels. In indoor environments, major sources of ethylbenzene are consumer products and cigarette smoke. Ethylbenzene is therefore ubiquitous in outdoor and indoor urban and rural air.

2.1 Physical, Chemical and Biological Properties

The physical and chemical properties of ethylbenzene are summarized in Table 2.

2.2 Environmental Fate

The environmental fate of ethylbenzene is summarized in Table 3. Fugacity predictions for ethylbenzene indicate that when released into the atmosphere, 99.57% of the compound will partition to air (ASTER, 1995).

Table 2 Physical and Chemical Properties of Ethylbenzene

Property	Value	Reference
Molecular Weight	106.16	Howard *et al.*, 1991; Budavari, 1996; WHO, 1996; NTP, 2001
Physical State	Liquid	Verschueren, 1983: WHO, 1996; Lewis, 1997; HSDB, 2003; NTP, 2001
Melting Point	-94.9	HSDB, 2003; RAIS, 2003
	-94.95	WHO, 1996
	-94.97	Verschueren, 1983; Howard *et al.*, 1991
	-95°C	ATSDR, 1999; NTP, 2001; OEHHA, 2003
Boiling Point	136.1°C	HSDB, 2003; RAIS, 2003
	136.2°C at 101.3 kPa	Howard *et al.*, 1991; NTP, 2001; Verschueren, 1983; WHO, 1996
Specific Gravity (liquid)	0.866 at 25°C/25°C	WHO, 1996; NTP, 2001
	0.867 at 20°C/4°C	HSDB, 2003; Verschueren, 1983
Specific Gravity (gas; air=1)	3.66	HSDB, 2003; NTP, 2001; Verschueren, 1983
Vapour Pressure	0.933 at 20°C	Verschueren, 1983
	1.24 at 20°C	WHO, 1996
	1.27 at 25°C	Howard *et al.*, 1991
	1.28 at 25°C	HSDB, 2003: RAIS, 2003
	1.6 at 30°C	Verschueren, 1983
Solubility in Water	138 mg/L at 15°C	WHO, 1996
	140 mg/L at 15°C	Verschueren, 1983
	152 mg/L at 20°C	Verschueren, 1983: WHO, 1996
	160 mg/L at 25°C	Amoore and Hautala, 1983
	161 mg/L at 25°C	Howard *et al.*, 1991
Solubility	Soluble in sulphur dioxide, ether, alcohol and most organic solvents	HSDB, 2003; NTP, 2001; WHO, 1996
	Slightly soluble in chloroform and water	HSDB, 2003; NTP, 2001; WHO, 1996
	Insoluble ammonia	HSDB, 2003; NTP, 2001
Henry's Law Constant	0.00788 atm.m^3/mol at 25°C	HSDB, 2003
	0.00844 atm.m^3/mol at 25°C	Howard *et al.*, 1991; ATSDR, 1999
Octanol Water Partitioning Coefficient (log K_{ow})	3.13	ATSDR, 1999; WHO, 1996
	3.15	ATSDR, 1999; Howard *et al.*, 1991; HSDB, 2003; RAIS, 2003; Verschueren, 1983
	4.34	ATSDR, 1999
Octanol Carbon Partitioning Coefficient (log K_{oc})	1.98-3.04	Mackay *et al.*, 1992; WHO, 1996
	2.21	Howard, 1989
	2.22	Chiou *et al.*, 1983
	2.38	Hodson and Williams, 1988

Property	Value	Reference
Flash Point (closed cup)	21°C	ATSDR, 1999; DHSS, 2002
Explosive Limits	1.2% to 6.8%	NTP, 2001
Autoignition Temperature	432°C	ATSDR, 1999; NTP, 2001
Odour Threshold	2 mg/m^3	WHO, 1996
	2-2.6 mg/m^3	Verschueren, 1983
	0.4-78.3 mg/m^3	van Gemert, 1999
	10 mg/m^3	Amoore and Hautala, 1983
	39.15 mg/m^3	Cometto-Muniz and Cain, 1995
Bioconcentration Factor	15	HSDB, 2003
-Fish	2.31	Herman *et al.*, 1991
-Algae		
Conversion Factors for Vapour (at 25°C and 101.3 kPa)	1 ppm = 4.35 mg/m^3 1 mg/m^3 = 0.23 ppm	Verschueren, 1983; WHO, 1996

Table 3 Environmental Fate of Ethylbenzene (based on ATSDR, 1999; Howard *et al.*, 1991; HSDB, 2003; Mackay *et al.*, 1992)

System	Fate	Half-life
Water	Loss by volatilization, biodegradation and adsorption to sediment or suspended particulate matter; photolysis, hydrolysis, bioconcentration and bioaccumulation are negligible	*Volatilisation*: 1.1 hours (model river) and 99 hours (model lake) *Aqueous aerobic degradation*: 72 to 240 hours
Soil	Loss by volatilization and adsorption; biodegradation may also occur; photolysis and hydrolysis are negligible; moderate mobility; potential for leaching	*Aqueous aerobic degradation*: 72 to 240 hours
Air	Exists solely as a vapour; degradation *via* reaction with hydroxyl radicals; photolysis and hydrolysis are negligible; may contribute to photochemical smog formation	*Photochemical reactions with hydroxyl radicals*: 0.5 hours to two days

Given its high vapour pressure, ethylbenzene is expected to exist solely as a vapour in the ambient atmosphere. It is degraded in the atmosphere primarily *via* reaction with photochemically-produced hydroxyl radicals (Atkinson *et al.* 1978; HSDB, 2003). The photooxidation half-life for this reaction in air is reported to vary between 0.5 hours to two days (Howard *et al.*, 1991). This reaction with hydroxyl radicals results in a short atmospheric lifetime and also limits the atmospheric transport of this substance (Dewulf and van Langenhove, 1997). Ethylbenzene also undergoes photooxidation reactions with nitrate radicals (Atkinson *et al.*, 1987), atomic oxygen (Grovenstein and Mosher, 1970; Herron and Huie, 1973) and ozone (Atkinson and Carter, 1984), albeit to a lesser degree than reaction with hydroxyl radicals. An atmospheric half-life of 2.7 days was estimated for all photooxidation reactions (ATSDR, 1999). Direct photolysis is not anticipated as ethylbenzene does not significantly absorb light above 290 nm (Howard *et al.*, 1991).

The photooxidation of ethylbenzene can produce peroxyacetyl nitrate, ethylphenol, benzaldehyde, acetophenone and ethylnitrobenzenes, and may contribute to the formation of photochemical smog in the troposphere (WHO, 1996). One particular by-product of ethylbenzene photodegradation is peroxyacetyl nitrate (PAN), which is a known irritant component of photochemical smog. However, ethylbenzene has a relatively low smog formation potential relative to alkenes, as it is less photochemically reactive (ATSDR, 1999). Yanagihara *et al.* (1977) report that its photoreactivity is intermediate to other volatile organic compounds.

Given its relatively low water solubility and high vapour pressure, little ethylbenzene is removed from the atmosphere *via* wet deposition (WHO, 1996). However, some ethylbenzene may sorb onto atmospheric particulate matter, which can be removed *via* precipitation or dry deposition.

Volatilization of ethylbenzene from moist soils and water surfaces is expected to be an important fate process based on its Henry's Law constant. Ethylbenzene also exhibits the potential for significant volatilization from dry soil surfaces due to its high vapour pressure (HSDB, 2003). In soil, ethylbenzene is moderately mobile and may leach into the groundwater, especially in soils with low organic carbon and clay content (Howard *et al.*, 1991). Ethylbenzene is considerably less mobile in soils with high organic carbon and/or clay content. Biodegradation in soil occurs primarily *via* nitrate reducing processes (HSDB, 2003). The kinetics of ethylbenzene biodegradation are site specific and depend upon such factors as the type and population of microbes present, the environmental temperature, the concentration of ethylbenzene, the presence of other compounds that may act as a substrate and the amount of oxygen and electron acceptors present. Ethylbenzene will not hydrolyze in soil due to the lack of hydrolyzable functional groups (Howard *et al.*, 1991; Mackay *et al.*, 1992).

In water, ethylbenzene volatilizes within a few hours to a few weeks, depending on local conditions (Howard, 1989). An average volatilization half-life from surface water is 3.1 hours (Thomas, 1982). The volatilization half-lives for a model river and model lake are 1.1 hours and 99 hours, respectively (HSDB, 2003). The high Henry's law constant for ethylbenzene indicates that a significant proportion of ethylbenzene will partition from water into air (Masten *et al.*, 1994), until its saturated vapour concentration is reached in air. Photolysis and hydrolysis of ethylbenzene in water is minimal (Howard, 1989; WHO, 1996). Transformations may also occur in water *via* photooxidation and biodegradation. While ethylbenzene does not directly absorb light wavelengths, it can undergo photooxidation reactions in water that are mediated through an indirect reaction with other light-absorbing molecules, such as humic acids (ATSDR, 1999). The aqueous aerobic biodegradation half-life of ethylbenzene in water is reported to range from 72 to 240 hours (Howard *et al.*, 1991; Mackay *et al.*, 1992). Anaerobic degradation of ethylbenzene may occur slowly in sediments (Howard, 1989).

Based on its log K_{ow} and sorption partitioning coefficient, ethylbenzene is expected to exhibit only moderate adsorption to suspended solids and sediments (HSDB, 2003). Dewulf *et al.* (1996) demonstrated that the sorption process of ethylbenzene on marine sediments is reversible and

occurs to a lower degree than expected based on its log K_{ow} value and the organic carbon content of sediments. These authors concluded that the marine sediment compartment is not an important sink for ethylbenzene.

According to the bioconcentration factor for ethylbenzene, the potential for bioconcentration in aquatic organisms is low (HSDB, 2003). Ethylbenzene does not significantly bioaccumulate in aquatic or terrestrial food chains (ATSDR, 1999).

3.0 EMISSION SOURCES, INVENTORIES AND AMBIENT AIR CONCENTRATIONS

3.1 Natural Sources

Ethylbenzene is a naturally occurring component of crude oil (WHO, 1996). Also, it is formed during combustion of organic materials; thus forest, grass and other biomass fires will release ethylbenzene to the atmosphere.

3.2 Anthropogenic Sources and Emissions Inventory

3.2.1 Industrial

Production processes, as well as industrial, commercial and domestic sources and uses of ethylbenzene were described in Section 2.0.

A total of 58 industrial facilities in Alberta reported on-site releases of ethylbenzene to the 2001 National Pollutant Release Inventory (NPRI) database. Of the total reported environmental releases of ethylbenzene, the majority is released to the atmosphere although a number of facilities in Alberta also release ethylbenzene to land or only release to land (NPRI, 2001).

Table 4 provides total on-site releases for the top 10 facilities in Alberta that release ethylbenzene to air, and Table 5 provides details on the air emissions for these facilities. The major sector in Alberta that releases ethylbenzene to air is the oil and gas sector, with the top contributors including oil sands operations, petroleum refineries, petrochemical plants and gas plants. For the majority of these facilities, fugitive emissions comprise the most significant portion of ethylbenzene emissions to air, although stack emissions are the major source for the Chevron Canada Resources and Paramount Resources facilities. Table 5 also shows that releases to air during storage and handling can be a significant source of ethylbenzene emissions for some facilities (*e.g.*, Conoco Canada Resources and Petro-Canada and Imperial Oil refineries in Edmonton).

3.3 Ambient Air Concentrations in Alberta

Alberta Environment has conducted a number of air quality monitoring surveys over the past several years in various regions of Alberta. Some of these surveys have reported ambient air concentrations of ethylbenzene. For example, a survey conducted from October 2000 to June 2001 in the Whitemud Drive area of Edmonton reported that one-hour average ambient air concentrations of ethylbenzene ranged from <2 to 17 $\mu g/m^3$ (AENV, 2002a). A VOC survey in the Fort Saskatchewan/Redwater area (AENV, 2003) conducted from May 2001 to February 2002 reported one-hour average ethylbenzene air concentrations to range from 0.06 to 0.96 $\mu g/m^3$ (average = 0.32 $\mu g/m^3$). A survey conducted in the Town of Banff in November 2002 reported one-hour average ethylbenzene concentrations on two sampling days of 0.53 and 0.80 $\mu g/m^3$ (AENV, 2002b). One hour average concentrations of ethylbenzene were non-detectable in an air monitoring survey conducted in the Carstairs/Crossfield Area between December 1999 and March 2000 (AENV, 2000b). A study of VOC air concentrations was conducted in the County of Grande Prairie between 1998 and 2000 (AENV, 2001). At a regional

background location (Beaverlodge Agriculture Research Farm), 24 hour average ethylbenzene air concentrations ranged from <0.07 to 0.3 $\mu g/m^3$. Ethylbenzene air concentrations were also measured at stations near a number of gas plants, batteries and well sites. One hour average ethylbenzene concentrations were reported to range from <1.4 to 13.0 g/m^3. Twenty-four hour average ethylbenzene air concentrations were reported to range from <0.07 to 10.1 $\mu g/m^3$.

Table 4 Total On-site Releases (tonnes/year) of Ethylbenzene in Alberta (Ten Largest Contributors) According to NPRI, 2001

NPRI ID	Facility Name	City	Total Releases (tonnes/year)			
			Air	Land	Water	Total
2274	Syncrude Canada Ltd. - Mildred Lake Plant Site	Fort McMurray	70.09	0	0	70.09
2230	Suncor Energy Inc. - Suncor Energy Inc. Oil Sands	Fort McMurray	41.28	0	0	41.28
2963	Shell Chemicals Canada Ltd. - Scotford Chemical Plant	Fort Saskatchewan	16.79	0	0	16.79
0683	Chevron Canada Resources - Kaybob South #3 Gas Plant	Fox Creek	11.13	0	0	11.13
2960	Shell Canada Products - Shell Scotford Refinery	Fort Saskatchewan	3.08	1.29	0	4.37
3903	Petro-Canada - Edmonton Refinery	Edmonton	1.16	1.88	0	3.04
3707	Imperial Oil – Strathcona Refinery	Edmonton	1.92	0.33	0	2.26
3941	Novagas Canada Limited Partnership - Harmattan Gas Plant	Olds	1.29	0	0	1.29
5389	Conoco Canada Resources Ltd. - Peco Plant	Edson	1.11	0	0	1.11
3754	Paramount Resources Limited - Kaybob Gas Plant	Fox Creek	0.98	0	0	0.98

Table 5 **Air Emissions of Ethylbenzene (tonnes/year) for Ten Largest Contributors in Alberta According to NPRI, 2001**

NPRI ID	Facility Name	City	Air Emissions (tonnes/year)					
			Stack/ Point	Storage/ Handling	Fugitive	Spills	Other	Total
2274	Syncrude Canada Ltd. - Mildred Lake Plant Site	Fort McMurray	0.89	2.94	66.26	0	0	70.09
2230	Suncor Energy Inc. - Suncor Energy Inc. Oil Sands	Fort McMurray	0.88	0.50	39.90	0	0	41.28
2963	Shell Chemicals Canada Ltd. - Scotford Chemical Plant	Fort Saskatchewan	0	2.27	14.52	0	0	16.79
0683	Chevron Canada Resources - Kaybob South #3 Gas Plant	Fox Creek	11.13	0	0	0	0	11.13
2960	Shell Canada Products - Shell Scotford Refinery	Fort Saskatchewan	0	0.25	2.83	0	0	3.08
3903	Petro-Canada - Edmonton Refinery	Edmonton	0	0.42	0.74	0	0	1.16
3707	Imperial Oil - Strathcona Refinery	Edmonton	0.10	0.89	0.93	0	0.01	1.92
3941	Novagas Canada Limited Partnership - Harmattan Gas Plant	Olds	0.01	0.00	1.28	0	0	1.29
5389	Conoco Canada Resources Ltd. - Peco Plant	Edson	0	0.63	0.48	0	0	1.11
3754	Paramount Resources Limited - Kaybob Gas Plant	Fox Creek	0.94	0	0.04	0	0	0.98

4.0 EFFECTS ON HUMANS AND ECOLOGICAL RECEPTORS

4.1 Humans and Experimental Animals

The following toxicological review of ethylbenzene is focussed primarily on the inhalation route of exposure, as this is the predominant route of human exposure to ethylbenzene in air. Data on other exposure routes are included in this review only where considered relevant or where inhalation exposure data are lacking. Where sufficient data are available, human studies are emphasized in this section. However, relevant experimental animal studies are included where human data is either lacking or inadequate.

4.1.1 Overview of Toxicokinetics of Ethylbenzene

Absorption

Inhalation studies in humans have found that ethylbenzene is rapidly and efficiently absorbed *via* this route. Human absorption of ethylbenzene by inhalation has been reported to range from 49 to 64% (Bardodej and Bardodejova, 1970; Gromiec and Piotrowski, 1984; Astrand *et al.*, 1978).

Animal inhalation studies have observed similar absorption efficiencies. Harlan-Wistar rats were found to rapidly absorb radiolabelled ethylbenzene, with an absorption efficiency of 44% (Chin *et al.*, 1980a, b). However, ATSDR (1999) noted that this absorption value may have been slightly overestimated, as possible contributions from dermal exposure were not addressed in this study.

Distribution

No studies were identified regarding the distribution of ethylbenzene in humans following inhalation exposure. A study by Pierce *et al.* (1996) suggests that *in vitro* partitioning of ethylbenzene from air into human adipose tissue is similar to that observed in rats.

Ethylbenzene has been shown to be efficiently distributed throughout the body in rats following inhalation exposure to radiolabelled ethylbenzene (Chin *et al.*, 1980b). The greatest amounts of ethylbenzene have been found in liver, the gastrointestinal tract, kidney and adipose tissue (Chin *et al.*, 1980b; Climie *et al.*, 1983). Due to its lipophilic nature, accumulation of ethylbenzene in adipose tissue appears to increase with increasing inhalation exposure concentrations (Engstrom *et al.*, 1985). However, this increase was not linear. The lack of linearity was partially attributed to the induction of metabolic enzymes that occurs with increasing exposure concentrations, as well as altered blood flow to adipose tissue, changes in lung excretion and changes in the distribution of ethylbenzene in different tissues.

Metabolism

Once absorbed and distributed in the body, ethylbenzene rapidly undergoes a complex series of biotransformations in humans and laboratory animals. While ethylbenzene metabolism varies between species, sex and depending on nutritional status, it does not appear to differ significantly

between exposure routes (ATSDR, 1999). The majority of ethylbenzene metabolism appears to occur in the liver and the adrenal cortex (Sullivan *et al.*, 1976; Greiner *et al.*, 1976).

Ethylbenzene is metabolized mainly through hydroxylation and then through conjugation reactions from which numerous metabolites have been isolated. In humans exposed by inhalation, the major metabolites of ethylbenzene are mandelic acid (64-71%) and phenylglyoxylic acid (19-25 %) (Bardodej and Bardodejova, 1970; Engstrom *et al.*, 1984). These studies also reported that urinalysis indicated approximately 70% and 25% of the retained dose of ethylbenzene was excreted in the urine as mandelic acid and phenylglyoxylic acid, respectively. Other metabolites of ethylbenzene detected in human urine include 1-phenylethanol (4%), p-hydroxyacetophenone (2.6%), m-hydroxyacetophenone (1.6%), and trace amounts of 1-phenyl- 1,2-ethanediol, acetophenone, 2-hydroxyacetophenone and 4-ethylphenol (Bardodej and Bardodejova, 1970; Engstrom *et al.*, 1984).

As in humans, the principal metabolic pathway in rats is believed to begin with hydroxylation (Climie *et al.*, 1983; Engstrom, 1984; Engstrom *et al.*, 1985). In rats exposed either by inhalation or orally to ethylbenzene, the major metabolites were identified as hippuric and benzoic acids (approximately 38%), I-phenylethanol (approximately 25%), and mandelic acid (approximately 15-23%), with phenylglyoxylic acid accounting for only 10% of the metabolites (Climie *et al.*, 1983; Engstrom, 1984; Engstrom *et al.*, 1985). Some studies have found that 4-ethylphenol and 2-hydroxyethylbenzene can also be produced from the metabolism of ethylbenzene (Bakke and Scheline, 1970; Kaubisch *et al.*, 1972). In rabbits, the most important metabolite is hippuric acid, which is believed to be formed by oxidative decarboxylation of phenylglyoxylic acid (El Masri *et al.*, 1958). Thus, there are no animal models of ethylbenzene metabolism that are completely consistent with human metabolism of this substance. However, rats appear to be a more appropriate model than rabbits for studying both toxicokinetics and toxicity of ethylbenzene in humans (ATSDR, 1999). In all species, ethylbenzene metabolites and intermediates are typically conjugated to form sulfates and glucuronides prior to excretion in urine (Engstrom *et al.*, 1984). Generally, these ethylbenzene metabolites and intermediates are believed to be of relatively low toxic potency (Bardodej and Bardodejova, 1970).

The nutritional status of animals has been shown to have a marked effect on ethylbenzene metabolism in rats (Nakajima and Sato, 1979). These authors found that the *in vitro* metabolic activity of liver microsomal enzymes on ethylbenzene was shown to be significantly enhanced in fasted rats despite a marked loss in liver weight.

Elimination and Excretion

Urinary excretion has been shown to be the primary route of elimination of ethylbenzene metabolites in both humans and experimental animals following oral or inhalation exposures (ATSDR, 1999). The pattern of excretion following dermal exposure in humans appears to differ significantly from that observed with oral and inhalation exposures. Dutkiewicz and Tyras (1967) observed only 4.6% of the dermally absorbed dose of ethylbenzene (as mandelic acid) in the urine. Interpretation of this study was difficult, due to the small percentage of absorbed dose accounted for and the lack of dermal exposure animal studies to support or refute the findings (ATSDR, 1999).

In human volunteers, elimination of the primary ethylbenzene metabolite, mandelic acid, was reported to be rapid, with the metabolite detected in the first urine sample following a 6-10 hour inhalation exposure to 0, 4, 8, 18, 35 or 46 ppm (0, 17.4, 34.8, 78.3, 152.3 or 200 mg/m^3) ethylbenzene (Gromiec and Piotrowski, 1984). The elimination of mandelic acid was reported to be biphasic, with half-lives of 3.1 hours for the rapid phase and 25 hours for the slower phase (Gromiec and Piotrowski, 1984). The metabolic efficiency, as indicated by excretion of mandelic acid, was reported to be independent of the exposure dose.

The elimination of ethylbenzene metabolites is also rapid in animals, and occurs primarily *via* the urine (Chin *et al.*, 1980a, b; Engstrom, 1984; Engstrom *et al.*, 1985). Rats exposed to 230 ppm (1,000 mg/m^3) radiolabelled ethylbenzene for six hours *via* inhalation excreted 91% of the radioactivity within 24 hours after the onset of exposure (Chin *et al.*, 1980a, b). In a similar inhalation experiment, rats exposed to 300 or 600 ppm (1,305 or 2,610 mg/m^3) had urinary excretion rates (percent of absorbed dose) of 83% and 59% respectively, within 48 hours after the onset of exposure (Engstrom, 1984). Approximately 13% of the absorbed dose was eliminated in the urine during the first six hours of exposure. Limited excretion of ethylbenzene metabolites has also been found to occur *via* the feces and expired air (Chin *et al.*, 1980b). There have also been differences observed between species in the relative proportion of metabolites excreted in the urine (Chin *et al.*, 1980a). Up to 5% of retained ethylbenzene is estimated to be exhaled in an un-metabolized form (Åstrand *et al.*, 1978).

Physiologically-Based Pharmacokinetic (PBPK) Models

Only two PBPK models for ethylbenzene were identified in the scientific literature (*i.e.*, Shatkin and Brown, 1991; Tardif *et al.*, 1997). The Shatkin and Brown model is limited to describing the toxicokinetics of the dermal route of exposure to ethylbenzene in aqueous solution. The developers of the model state that it has potentially useful applications for risk assessment if used within its limitations. The model was found to be capable of predicting 94% of experimental results with humans under the same conditions simulated in the model.

The Tardif *et al.* (1997) model is intended to simulate toxicokinetics following exposure to a mixture of alkyl benzenes and is based on existing individual PBPK models for toluene, m-xylene and ethylbenzene. Each individual model consists of a liver, fat, richly and poorly perfused tissue compartments, and assumes that compounds are exclusively metabolized in the liver compartment. The individual models for each compound are linked together through a term representing hepatic metabolism. No other PBPK models were identified that simulate toxicokinetics following inhalation of ethylbenzene.

Mechanism of Toxic Action

Animal studies indicate that the mode of ethylbenzene neurotoxicity at the cellular level involves changes in neurotransmitter levels (*e.g.*, dopamine), other biochemical changes and altered evoked electrical activity in the brain (Andersson *et al.*, 1981; Frantik *et al.*, 1994; Mutti *et al.*, 1988; Romanelli *et al.*, 1986). A number of *in vitro* studies suggest that the mechanism of toxicity for ethylbenzene is changes in the structure, integrity and permeability of cell membranes resulting from the partitioning of ethylbenzene into the phospholipid bilayer of cell membranes (Engelke *et al.*, 1993; Naskali *et al.*, 1993, 1994; Sikkema *et al.*, 1995; Vaalavirta

and Tahti, 1995a, b). Such changes in the integrity of the cell membrane may alter membrane structure and function, including changes in permeability, energy transduction, protein matrix, ion transport and enzyme inhibition (Vaalavirta and Tahti, 1995a, b; Naskali *et al.*, 1994).

Biomarkers

Potential biomarkers of exposure to ethylbenzene include mandelic acid and phenylglyoxylic acid in urine, and direct detection of ethylbenzene in whole human blood, adipose tissue and breast milk (ATSDR, 1999). Ethylbenzene concentrations in exhaled breath samples from human subjects were also reported to correlate well with ethylbenzene air concentrations measured with personal air monitors (Wallace *et al.*, 1984).

Of these potential biomarkers of exposure, mandelic acid in urine is recommended as a biological index of exposure by the ACGIH. However, it should be recognized that mandelic acid is also a metabolite of styrene (ATSDR, 1999) as well as certain drugs (Aitio *et al.*, 1994); thus, its presence in urine is not necessarily indicative of recent ethylbenzene exposure, especially if there is concurrent exposure to styrene or drugs are being taken which metabolize to mandelic acid. A personal exposure monitoring study by Inoue *et al. (*1995) found that low ethylbenzene air concentrations (approximately 8.6 mg/m^3 (2 ppm)) correlated well with urinary phenylglyoxylic acid concentrations, suggesting that measurements of this acid in the urine could also be used for biomonitoring.

No specific biomarkers of effect were identified for ethylbenzene in the available scientific literature (ATSDR, 1999).

4.1.2 Acute Toxicity

In humans, the symptoms of acute ethylbenzene intoxication following inhalation exposure include: respiratory tract and ocular irritation, lacrimation (tearing), chest constriction, a burning sensation, dizziness, vertigo and minor hematological changes (ATSDR, 1999; WHO, 1996). The principal target organs of ethylbenzene appear to be the upper respiratory tract, eyes, lungs, liver and kidney, with transient effects on the hematological system (ATSDR, 1999).

Cometto-Muniz and Cain (1995) studied eye irritation and odour thresholds for ethylbenzene. Testing sessions lasted one to two hours starting with the highest air concentration. Eye irritation thresholds for ethylbenzene were found to be well above the odour thresholds. Eye irritation occurred at 10,000 ppm (43,500 mg/m^3), whereas the odour threshold was found to occur at 9 ppm (39 mg/m^3).

In an early study (Yant *et al.*, 1930), throat irritation, chest constriction, dizziness and vertigo were reported in six male volunteers acutely exposed to an ethylbenzene air concentration of 2,000 ppm (8,700 mg/m^3). These symptoms increased in severity when the exposure level was 5,000 ppm (21,750 mg/m^3). Temporary ocular irritation, a burning sensation and profuse lacrimation were reported by the test subjects at 1,000 ppm (4,350 mg/m^3). No other significant respiratory changes were reported. The subjects showed complete recovery from these symptoms upon cessation of exposure. ATSDR (1999) notes that the utility of these study results is limited because the exposure durations were not clearly described and the ethylbenzene used for testing

reportedly contained trace impurities (*e.g.*, benzol and diethylbenzene). Also, the methods used to calculate the vapour concentration of ethylbenzene were not well described, making it difficult to verify their accuracy.

No respiratory effects were observed in a male and female patient exposed to 55.3 ppm (240.6 mg/m^3) ethylbenzene for 15 minutes in an inhalation chamber (Moscato *et al.*, 1987).

Symptoms of acute ethylbenzene toxicity in experimental animals are similar to those observed in humans in that eye and respiratory tract irritation is frequently reported, but acute toxicity in animals is also manifested by neurological and neurobehavioral effects, hearing impairment, altered liver and kidney enzyme levels and increased liver weights.

Overall, ethylbenzene appears to be of relatively low acute toxicity in animals. Inhalation LC50 values for rats exposed after four and two hours were 4,000 ppm (17,400 mg/m^3) and 13,367 ppm (58,146 mg/m^3), respectively (Smyth *et al.*, 1962; Ivanov, 1962). The concentrations causing 100% mortality in rats were 8,000 ppm (34,800 mg/m^3) after four hours (Smyth *et al.*, 1962) and 16,698 ppm (72,636 mg/m^3) after two hours (Ivanov, 1962). ATSDR (1999) notes that the results of both of these studies have limited use, as the recorded ethylbenzene concentrations were not analytically verified. The acute lethality of ethylbenzene has been reported to vary among experimental animals, with mice being the most sensitive (ATSDR, 1999; Cragg *et al.*, 1989).

Cavender (1993) reported that inhalation of ethylbenzene for three minutes at a concentration of 4,300 mg/m^3 caused slight nasal irritation in guinea pigs. An eight-minute exposure to this concentration caused eye irritation in addition to nasal irritation. Both effects also occurred at a one-minute exposure to 8,600 mg/m^3.

In the study by Yant *et al.* (1930), similar ocular and nasal effects to those observed in humans were seen in guinea pigs. Eye irritation accompanied by tearing and nasal irritation was observed in guinea pigs three and eight minutes after exposure to 1,000 ppm (4,350 mg/m^3) ethylbenzene, and one minute after exposure to ethylbenzene concentrations ranging from 2,000 to 10,000 ppm (8,700 to 43,500 mg/m^3). Nasal irritation was also noted in guinea pigs exposed to 2,000, 5,000 and 10,000 ppm (8,700, 21,750 and 43,500 mg/m^3) for 480, 30 and 10 minutes, respectively. At concentrations above 2,000 ppm (8,700 mg/m^3), central nervous system depression and ataxia were also observed. Gross histopathological examination revealed congestion and edema in the lungs, with an increase in the severity of these effects with increasing exposure concentrations.

The air concentration of ethylbenzene required to decrease the respiratory rate in mice by 50% (RD50) was reported to be 1,432 ppm (6,229 mg/m^3) in male Swiss OFi mice (De Ceaurriz *et al.*, 1981) and 4,060 ppm (17,660 mg/m^3) in Swiss Webster mice (De Ceaurriz *et al.*, 1981; Nielsen and Alarie, 1982). Respiratory depression was reported in Swiss Webster mice after intratracheal administration of 4,000 ppm (17,400 mg/m^3) ethylbenzene for 30 minutes (Nielsen and Alarie, 1982).

Toftgard and Nilsen (1982) reported increased liver-to-body-weight ratios in male Sprague-Dawley rats exposed to 2,000 ppm (8,700 mg/m^3) ethylbenzene for three days. A number of kidney and liver enzymatic changes were also reported at this exposure level, including increased concentrations and activities of 7-ethoxycoumarin, 0-deethylase, UDP glucuronyl-transferase, NADPH cytochrome c reductase, cytochrome P-450, 7-ethoxyresorufin.

Cragg *et al.* (1989) reported that F344 rats displayed lacrimation after four days of inhalation exposure to 1,200 ppm (5,220 mg/m^3) ethylbenzene, while B6C3F1 mice and New Zealand White rabbits showed lacrimation at 400 ppm (1,740 mg/m^3). Salivation, prostration and/or reduced activity were also reported in rats and mice exposed to 2,400 or 1,200 ppm (10,440 or 5,220 mg/m^3) ethylbenzene, respectively. Rabbits exposed to 2,400 ppm ethylbenzene for the same duration showed no adverse behavioural effects. These authors also reported that after four weeks of exposure to 382 ppm (1,662 mg/m^3), rats showed only sporadic lacrimation, while mice and rabbits showed no adverse ocular effects at ethylbenzene air concentrations of 782 ppm and 1,610 ppm (3,400 and 7,000 mg/m^3), respectively.

Tegeris and Balster (1994) studied the neurobehavioral effects of ethylbenzene in adult male CFW albino mice exposed to 0, 2,000, 4,000 or 8,000 ppm (0, 8,700, 17,400 or 34,800 mg/m^3) for 20 minutes. All tested concentrations produced changes in posture, decreased arousal and rearing, increased ease of handling, gait disturbances, reduced mobility and righting reflex, decreased forelimb grip strength, increased landing foot splay, decreased sensory-motor reactivity and impaired psychomotor coordination. The authors also observed lacrimation and palpebral closure in mice exposed to these air concentrations. These effects were short-lived and were most pronounced during exposure than after exposure. Recovery was noted to occur within minutes of removal from the exposure chamber.

Changes in dopamine and other biochemical parameters associated with neurotoxicity have been reported in Sprague-Dawley rats exposed to 2,000 ppm (8,700 mg/m^3) ethylbenzene (Andersson *et al.*, 1981) and New Zealand White rabbits exposed to 750 ppm (3,263 mg/m^3) ethylbenzene (Mutti *et al.*, 1988; Romanelli *et al.*, 1986) for three to seven days. Frantik *et al.* (1994) found that exposure of rats and mice to 245 and 342 ppm (1,066 and 1,488 mg/m^3), respectively, produced a 30% depression in evoked electrical activity in the brain immediately after exposure.

A number of studies in recent years have investigated the effects of acute ethylbenzene exposure on hearing function in experimental animals. Cappaert *et al.* (1999) reported that exposure of rats to 800 ppm (3,480 mg/m^3) ethylbenzene for eight hours/day, over five days induced hearing loss due to outer hair cell loss. Cappaert *et al.* (2000) exposed rats to ethylbenzene at 0, 300, 400 and 550 ppm (0, 1,305, 1,740 and 2,393 mg/m^3) for eight hours/day for five consecutive days. Auditory function was tested three to six weeks post-exposure, and outer hair cell (OHC) loss was quantified by histological examination. At 300 ppm, there were no observed auditory effects. At 400 ppm, auditory thresholds were increased by 15 and 16 dB at 12 and 16 kHz, respectively, and at 550 ppm by 24, 31 and 22 dB at 8, 12 and 16 kHz, respectively. Distortion-product otoacoustic emission amplitude growth with stimulus level was found to be affected only at 550 ppm at 5.6, 8 and 11.3 kHz. At 400 ppm, a 25% OHC loss was found at the 11- and 21-kHz region. At 550 ppm, there was a 40% and 75% OHC loss at the 11- and 21-kHz locations,

respectively. It was concluded that the mid-frequency region of rat cochlea is affected by relatively low air concentrations of ethylbenzene (*i.e.*, 400 to 550 ppm (1,740 to 2,393 mg/m^3)).

The effects on rat hearing due to simultaneous exposure to ethylbenzene and broadband noise were evaluated by Cappaert *et al.* (2001). Three ethylbenzene air concentrations (0, 300 or 400 ppm; equivalent to 0, 1,305 or 1,740 mg/m^3) and three noise levels (95 or 105 dB(lin) SPL (sound pressure level), or background noise at 65 dB(lin) SPL) were tested in combination during a five day exposure for eight hours/day. The authors reported that distortion product otoacoustic emissions and compound action potentials were affected after 105 dB alone, and after 105 dB in combination with ethylbenzene at 300 and 400 ppm. However, the amount of loss for these combinations did not exceed the loss observed at 105 dB alone. Outer hair cell (OHC) loss after exposure to 300 ppm ethylbenzene was located in the third row of OHCs. At 400 ppm, the loss occurred in the second and first row of OHCs. Noise by itself caused minimal effects on the OHC counts except for a minor loss in the first row of OHCs after 105 dB SPL. Noise at 105 dB in combination with ethylbenzene at 300 and 400 ppm, produced an OHC loss that was greater than the sum of the losses induced by both noise and ethylbenzene alone (an apparent synergistic effect).

Cappaert *et al.* (2002) compared the ototoxic effects of ethylbenzene in guinea pigs and rats. Consistent with previous studies, rats showed deteriorated auditory thresholds in the mid-frequency range, after exposure to 550 ppm (2,393 mg/m^3) ethylbenzene for eight hours/day, over five days. Outer hair cell (OHC) loss was found in the corresponding mid-frequency cochlear regions. In contrast, guinea pigs showed no auditory threshold shifts and no OHC loss following exposure to much higher concentrations (*i.e.*, 2,500 ppm (10,875 mg/m^3) for six hours/day over five days). Four rats and four guinea pigs were subsequently evaluated in an attempt to understand this species difference in susceptibility. Ethylbenzene concentrations in blood were determined in both species after exposure to 500 ppm ethylbenzene for eight hours/day over three days. After day 1, rat blood contained 23.2 µg/ml ethylbenzene, while guinea pig blood contained 2.8 µg/ml. By day 3, the ethylbenzene concentration in rat blood was still 4.3 times higher than that in guinea pigs. The authors suggest that this species difference in auditory susceptibility to ethylbenzene may be related to blood levels and differences in metabolism between guinea pigs and rats. It is presently unclear what the implications of the rat hearing studies are for humans exposed to ethylbenzene.

Although no studies were located regarding the effect of nutritional status on ethylbenzene toxicity, it has been postulated that food deprivation may decrease toxicity since detoxification reactions for ethylbenzene are increased significantly in fasted rats relative to fed rats (Nakajima and Sato, 1979).

Tables 6 and 7 provide a summary of the acute human and experimental animal inhalation toxicity studies with ethylbenzene.

Table 6 Summary of Acute Human Toxicity Studies with Ethylbenzene

Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
1 to 2 h	43,500	- Eye irritation threshold	Cometto-Muniz and Cain, 1995
15 minutes	240.6	- No respiratory effects	Moscato et al., 1987

Table 7 Summary of Acute Inhalation Studies with Ethylbenzene in Experimental Animals

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Guinea pigs	3 minutes	4300	- slight nasal irritation	Cavender, 1993
	8 minutes	4300	- eye and nasal irritation	
	1 minute	8600	- eye and nasal irritation	
Guinea pigs	3 minutes	4350	- eye and nasal irritation	Yant et al., 1930
	1 minute	8700	- eye and nasal irritation	
	480 minutes	8700	- nasal irritation CNS depression and ataxia	
	30 minutes	21,750		
	10 minutes	43,500		
Mice	30 minutes	17,400 (intratracheal administration)	- respiratory depression	Nielsen and Alarie, 1982
Rats	3 d	8700	- increased liver-to-body weight ratios; kidney and liver enzymatic changes	Toftgard and Nilsen, 1982
Rats	4 d	5220	- lacrimation	Cragg et al., 1989
Mice	4 d	1740	- lacrimation	Cragg et al., 1989
Rabbits	4 d	1740	- lacrimation	Cragg et al., 1989
Mice	20 minutes	8700	- behavioural effects, lacrimation and palpebral closure; recovery occurred minutes after exposure	Tegeris and Balster, 1994
Rats	3 to 7 d	8700	- biochemical effects associated with neurotoxicity	Andersson et al., 1981
Rabbits	3 to 7 d	3263	- biochemical effects associated with neurotoxicity	Mutti et al., 1988 ; Romanelli et al., 1986
Rats	8 h / d over 5 d	3480	- hearing loss due to outer hair cell loss	Cappaert et al., 1999
Rat	8 h / d for 5 d	1740 to 2393	- effects to mid-frequency region of cochlea	Cappaert et al., 2000 ; Cappaert et al., 2002
Guinea pigs	8 h / d for 5 d	10,875	- no effects to auditory thresholds or outer hair cell loss	Cappaert et al., 2002

4.1.3 Subchronic and Chronic Toxicity

Human epidemiology studies investigating the subchronic or chronic toxicity of ethylbenzene *via* the inhalation route are limited. Furthermore, the available studies are inconclusive and suffer from a number of methodological and reporting limitations, and are confounded by concurrent exposures to other chemicals.

Angerer and Wulf (1985) evaluated 35 solvent-exposed workers (exposed for an average of 8.2 years) who sprayed varnishes containing alkyd-phenol and polyester resins dissolved in solvent mixtures consisting principally of xylene isomers and ethylbenzene. Some of the varnishes also contained lead-based pigments. Personal air monitors indicated an average ethylbenzene air concentration of 4.0 ppm (17.4 mg/m^3). The workers displayed significantly elevated lymphocytes and significantly decreased erythrocyte counts and haemoglobin levels relative to controls. While these results suggest that the hematopoietic system might be a target of ethylbenzene, the observed effects cannot be attributed solely to ethylbenzene since a number of other solvent compounds (*e.g.*, xylene, methylchloroform, n-butanol, toluene, C9 hydrocarbons) were also detected in workplace air (U.S. EPA, 1991; ATSDR, 1999). In addition, simultaneous exposure to lead in pigments may have been a confounding factor (ATSDR, 1999).

Bardodej and Cirek (1988) conducted a biomonitoring study of 200 ethylbenzene production workers occupationally exposed to unspecified air concentrations of ethylbenzene and benzene over a 20-year period (mean duration was 12.2 years). No statistically significant hematological or hepatic effects were observed in exposed workers relative to controls. As the ethylbenzene air concentrations were not specified in this study and there was concurrent exposure to benzene, the study results are of questionable use in understanding the human inhalation toxicity of ethylbenzene.

Subchronic and chronic inhalation studies with ethylbenzene in experimental animals have demonstrated a variety of adverse effects.

The NTP (1988; 1989; 1990; 1992) reported an inhalation toxicology study using 99% purity ethylbenzene and groups of male and female F344/N rats and $B6C3F_1$ mice. Test animals were exposed to ethylbenzene vapour at chamber concentrations of 0, 100, 250, 500, 750 or 1,000 ppm (0, 435, 1,088, 2,175, 3,263 or 4,350 mg/m^3), for six hours per day, five days per week for 13 weeks. There was no mortality in rats or mice during the 13-week exposure. Body weight gains were reduced in the high dose groups of both male and female rats, but the differences were not statistically significant. Significant concentration-related increases in absolute liver weights occurred in males at 250 ppm and higher. In females, the lowest concentration at which an increase in absolute liver weight was observed was the 500 ppm group. Relative liver weights were significantly increased in all male exposure groups except 100 ppm, while only the three highest female exposure groups showed significant increases in relative liver weights. Absolute kidney weights in males significantly increased only in the 500 and 750 ppm groups, with relative weights increased in the three highest exposure groups. In females, both absolute and relative kidney weights increased significantly in the three highest exposure groups only. No histopathologic changes were observed in any tissues of rats. Serum alkaline phosphatase (SAP) activity was significantly reduced in rats in a concentration-dependent manner (at 500 ppm and above) for both sexes. However, the significance of this

decrease is not clear since in liver damage, SAP levels usually increase (U.S. EPA, 1991). It was suggested by the study investigators that this SAP level decrease may have been due to reduced water and food intake. Regeneration of renal tubules in the kidneys of male rats was observed in all groups including controls, with severity greatest at the highest exposure level. The significance of this effect is not clear. The most significant gross observation reported for rats was the presence of enlarged bronchial and/or mediastinal lymph nodes; however, these observations were not dose-related. This effect was ultimately attributed to an infectious agent rather than ethylbenzene exposure (NTP, 1989). However, no infectious agent was identified upon serologic examination of the rats.

In the mice, no significant gross or histopathological observations were noted upon necropsy in any organs, including the lung. The only exposure-related effects in mice were significantly elevated absolute and relative liver weights in both sexes in the 750 and 1,000 ppm groups, and significantly elevated relative kidney weights in females exposed to 1,000 ppm. There were no significant histopathological changes or impaired function observed in the liver or kidney of either sex. NTP (1992) concluded that there is minimal toxicity in F344/N rats and $B6C3F_1$ mice exposed to ethylbenzene by inhalation for 13 weeks at concentrations up to 1,000 ppm (4,350 mg/m^3).

NTP (1999) also conducted a two-year study of ethylbenzene toxicity in rats and mice. The study was designed to examine the potential carcinogenic effects of ethylbenzene, although non-carcinogenic endpoints were also examined. The non-carcinogenic effects are described below while the carcinogenic effects are described in Section 4.1.6. In the rat study, groups of 50 male and female F344/N rats were exposed to 0, 75, 250 or 750 ppm (0, 326, 1,088 or 3,263 mg/m^3) ethylbenzene by inhalation, six hours per day, five days per week, for 104 weeks. Survival of male rats in the 750 ppm group was significantly reduced relative to controls. Mean male body weights in the 250 and 750 ppm groups were generally lower than in controls, beginning at week 20. Mean female body weights in all exposed groups were generally less than those in controls during the second year of the study. The incidence of renal tubule hyperplasia in the 750 ppm males was significantly greater than in controls. Detailed evaluation of the kidneys revealed a significant increase in the incidences of renal tubule hyperplasia in 750 ppm males and females. The severity of nephropathy in 750 ppm male rats, and all exposed female rats were significantly increased relative to controls.

In the mouse study, groups of 50 male and female $B6C3F_1$ mice were exposed to 0, 75, 250 or 750 ppm (0, 326, 1,088 or 3,263 mg/m^3) ethylbenzene by inhalation, six hours per day, five days per week, for 103 weeks. The incidence of alveolar epithelial metaplasia in 750 ppm males and the incidence of eosinophilic foci in 750 ppm females were significantly greater than in controls. There were a variety of non-neoplastic liver changes in exposed male mice, including syncytial alteration of hepatocytes, hepatocellular hypertrophy and hepatocyte necrosis. There was also an increased incidence of hyperplasia of the pituitary gland pars distalis in 250 and 750 ppm females, and thyroid gland follicular cell hyperplasia in 750 ppm males and females, relative to controls.

Based on an evaluation of all the non-cancer data in mice and rats from the NTP (1999) study, OEHHA (2003) selected 75 ppm (326 mg/m^3) as the NOAEL.

Clark (1983) exposed Wistar rats to 0 and 100 ppm (434 mg/m^3) ethylbenzene for six hours/day, five days/week for 12 weeks. The duration-adjusted values were reported to be 0 and 77.5 mg/m^3. No statistically significant effects were observed at 100 ppm. Slight bile duct hyperplasia was seen in 15 of 18 exposed males and 14 of 18 exposed females, but was common in controls (10 of 18 females and 8 of 18 males). There was no statistically significant difference between exposed and control rats for this effect. The results of this study suggest a NOAEL of 100 ppm (434 mg/m^3), which equates to a human equivalent concentration (HEC) of 77.5 mg/m^3 (U.S. EPA, 1991).

Wolf *et al.* (1956) exposed rats to 400, 600 or 1,250 ppm (1,737, 2,606 or 5,428 mg/m^3) ethylbenzene for seven hours/day, five days/week for a period of six to seven months. Duration-adjusted concentrations were reported to be 0, 362, 542 and 1,131 mg/m^3, respectively. Male rats were only exposed to 2,200 ppm (9,554 mg/m^3) for seven hours/day, five days/week for five months (duration-adjusted concentration was 1,990 mg/m^3). Growth was found to be moderately depressed in male rats in the 2,200 ppm group. Liver and kidney weights in rats were increased slightly in all exposure groups relative to controls. Rats exposed to 1,250 and 2,200 ppm also showed histopathological changes manifested as cloudy swelling of the liver and renal tubules and testicular degeneration. While the study results suggest a NOAEL for lack of liver histopathological effects at 600 ppm, incidence data for these effects was not reported. Given this reporting limitation as well as uncertainty over whether the observed liver changes are adverse effects, a NOAEL or LOAEL cannot be identified (U.S. EPA, 1991).

This same study also exposed guinea pigs and rabbits to 0, 400 or 600 ppm (duration-adjusted concentrations of 0, 362 or 542 mg/m^3, respectively) ethylbenzene for seven hours/day, five days/week for roughly six months. In addition, females only were exposed to 1,250 ppm (duration-adjusted concentration of 1,131 mg/m^3). Growth was found to be depressed in female guinea pigs exposed to 1,250 ppm. Guinea pig liver weights were slightly increased in the 600 ppm group only. As this was not considered an adverse effect, the NOAEL for guinea pigs was determined to be 600 ppm (which equates to an HEC NOAEL of 542 mg/m^3). No adverse effects were observed in rabbits apart from a slight degeneration of the testicular germinal epithelium in males at 600 ppm. This study also exposed a single male Rhesus monkey to 600 ppm (duration-adjusted concentration of 542 mg/m^3) and two female monkeys to 400 ppm (duration-adjusted concentration of 362 mg/m^3). A slight degeneration of the testicular germinal epithelium and increased liver weight was observed in the male monkey, while no exposure-related effects were reported for the female monkeys. Due to the small number of monkeys in this experiment, a NOAEL or LOAEL cannot be identified.

Cragg *et al.* (1989) exposed B6C3F1 mice and F344 rats to ethylbenzene concentrations of 0, 99, 382 and 782 ppm (0, 430, 1,659 and 3,396 mg/m^3) for six hours/day, five days/week for four weeks. Duration-adjusted concentrations were reported to be 0, 77, 296 and 606 mg/m^3, respectively. In addition, New Zealand White rabbits were exposed to concentrations of 0, 382, 782 or 1,610 ppm (0, 1,659, 3,396 or 6,992 mg/m^3). The duration-adjusted concentrations were 0, 296, 606 and 1,249 mg/m^3, respectively. There were no observed changes in mortality, clinical chemistry parameters, urinalysis or incidence of gross or histopathological lesions. It should be recognized that the evaluation of the test animals was not consistent in this study. For

example, urinalysis was not performed on rabbits, clinical chemistry parameters were not evaluated in mice, and histopathology was only conducted on animals in the high exposure groups, with the exception that all male rabbit testes were examined. Rats in the 382 ppm group displayed sporadic incidences of salivation and lacrimation. Absolute liver weights were significantly increased in male rats in the 382 ppm group. Relative liver weight was increased in male rats at 782 ppm. In female rats, absolute liver weight was significantly increased at 782 ppm. Male rats in the 782 ppm group had a significant increase in platelets while female rats had a significant increase in total leukocytes. In mice, females showed a statistically significant increase in absolute, but not relative liver weights, at 782 ppm. There were no significant liver weight changes in male mice at any concentration. Rabbits showed no liver changes at any concentration. Based on a lack of adverse histopathological liver effects, a NOAEL of 782 ppm was identified for rats and mice, while a NOAEL of 1,610 ppm was identified for rabbits. When converted to human-equivalent concentrations, the HEC NOAEL values are 606 mg/m^3 when considering the mice and rat NOAEL, and 1,249 mg/m^3 when considering the rabbit NOAEL.

Elovaara *et al.* (1985) exposed male Wistar rats to 0, 50, 300 or 600 ppm (0, 217, 1,302 or 2,604 mg/m^3) ethylbenzene for six hours/day, five days/week for periods of two, five, nine or 16 weeks. The duration-adjusted values were reported as 0, 38.7, 233 and 465 mg/m^3, respectively. Concentration-dependent increases in drug-metabolizing enzymes of liver and kidney were found at all concentrations. There were no changes in liver weight at any concentration. After 16 weeks exposure, NADPH-cytochrome reductase and UDPG-transferase were significantly elevated in the 300 and 600 ppm groups. Aminopyrine N-demethylase and 7- ethoxycoumarin-0-deethylase (7-ECDE) were elevated at all exposure levels. The elevation in UDPG-transferase was exposure-dependent and was suggested by the study authors as possibly indicating glucuronidation of ethylbenzene metabolites. Electron microscopy showed changes in hepatocyte ultrastructure at all exposure levels, beginning two to nine weeks post-exposure, which were consistent with enzyme induction. There was no reported liver necrosis, increases in serum alanine aminotransferase or changes in hepatic glutathione (GSH) content. Significant increases in relative kidney weight were reported following weeks 2 and 9, but not following 16 weeks of exposure to 600 ppm. Kidney 7-ECDE and UDPG transferase activities showed statistically significant and exposure-related increases at all exposure levels.

As there was no histologic evidence of liver damage, and the changes in liver weights, enzyme levels and ultra structural changes are considered to be adaptations rather than adverse effects, a NOAEL of 600 ppm was suggested. This equates to an HEC NOAEL of 465 mg/m^3.

Table 8 summarizes the subchronic and chronic inhalation NOAELs, LOAELs, and other endpoints that were reported in the animal studies described above.

Table 8 Summary of Subchronic and Chronic Ethylbenzene Inhalation Toxicology Studies in Experimental Animals

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Rats	6 h/d, 5 d/wk for 13 wks	1088	- significantly elevated relative and absolute liver weights (males)	NTP, 1988; 1989; 1990; 1992
		2175	- significantly increased absolute and relative kidney weights (males and females)	
		2175	- significantly elevated absolute and relative liver weight (females)	
Mice	6 h/d, 5 d / wk for 13 wks	3263	- significantly elevated absolute relative liver weights (males and females)	NTP, 1988; 1989; 1990; 1992
		4350	- significantly elevated relative kidney weights (females)	
Rats	6 h/d, 5 d/wk for 103 wks	326	- NOAEL identified by OEHHA (2003) for non-cancer effects	NTP, 1999
Mice	6 h/d, 5 d/wk for 103 wks	326	- NOAEL identified by OEHHA (2003) for non-cancer effects	NTP, 1999
Rats	6 h/d, 5 d/wk for 12 wks	434	- NOAEL	Clark, 1983
Mice	6 h/d, 5 d/wk for 4 wks	3396 (606 duration adjusted)	- NOAEL for lack of adverse histopathological liver effects	Cragg et al., 1989
Rats	6 h/d, 5 d/wk for 4 wks	3396 (606 duration adjusted)	- NOAEL for lack of adverse histopathological liver effects	Cragg et al., 1989
Rabbits	6 h/d, 5 d/wk for 4 wks	6992 (1249 duration adjusted)	- NOAEL for lack of adverse histopathological liver effects	Cragg et al., 1989
Rats	6 h/d, 5 d/wk for 2, 5, 9 or 16 wks	2604 (465 duration adjusted)	NOAEL	Elovaara et al., 1985

4.1.4 Developmental and Reproductive Toxicity

No human studies were identified that investigated the reproductive or developmental effects of ethylbenzene following inhalation exposure.

Ungvary and Tatrai (1985) exposed CFY rats to 600, 1,200 or 2,400 mg/m^3 ethylbenzene for 24 hours/day during days 7 to 15 of gestation. In addition, CFLP mice were exposed to 500 mg/m^3 for 24 hours/day from gestational days 6 to 15, or for three days (intermittently) for four hours/day from gestational days 6 to 15. New Zealand white rabbits were also exposed for 24 hours/day to ethylbenzene concentrations of 500 or 1,000 mg/m^3 from gestational days 7 to 20. Untreated animals and animals exposed only to air served as controls. The study suffered from some inconsistent and insufficient documentation of results, such that it is not clear which particular experiment certain results pertain to (U.S. EPA, 1991). ATSDR (1999) also noted that the published version of this study has many deficiencies, including poor reporting of the experimental conditions used, absence of significant data concerning the test chemical and generation of the exposure environment, insufficient number of dose levels tested, and details of maternal and foetal observations, including abnormalities. Nonetheless, it is described below as

there are few developmental or reproductive toxicity studies available for ethylbenzene in experimental animals that used the inhalation route of exposure.

Maternal toxicity (species not stated) was reported to be moderate and concentration-dependent, but no data were presented. Maternal weight gain was reported to be decreased in rabbits exposed to 1,000 mg/m^3. Data were unavailable for developmental endpoints in the 1,000 mg/m^3 group because there were no live foetuses. In addition, one dam had died, three aborted and four had total foetal resorptions in this group. However, as similar effects were observed with four other test compounds, and other developmental toxicity studies with ethylbenzene did not report such effects, they were discounted as not being treatment-related. A significant reduction was noted in mean female foetal weight in rabbits exposed to 500 mg/m^3. In rats, post-implantation loss and skeletal retardation were significantly elevated ($p<0.05$) at all exposure levels except the 600 mg/m^3 group. However, this exposure level did produce foetal effects including increased incidence of dead/resorbed foetuses and lower weights of foetuses. In the 24-hour per day exposure experiment with rats, malformations characterized as "anomalies of the uropoietic apparatus" and an increased incidence of extra ribs were significantly increased at 2,400 mg/m^3. However, no specific data were presented on these malformations. The results from the continuous exposure rat experiment suggest a human equivalent LOAEL of 2,400 mg/m^3 for extra ribs in the absence of demonstrable maternal toxicity (U.S. EPA, 1991). In mice, an increased incidence of "anomalies of the uropoietic apparatus" was also reported, but again, no specific data were presented. There was no discussion concerning maternal toxicity in mice. Given the poor level of documentation in this study, it is possible that the observed foetal effects reported may have been due to maternal toxicity rather than developmental toxicity (Manson and Kang, 1989).

Andrew *et al.* (1981) conducted inhalation experiments with Wistar rats and New Zealand white rabbits exposed six to seven hours/day, seven days/week during days 1-19 and 1-24 of gestation, respectively, to 0, 100 or 1,000 ppm ethylbenzene (0, 434 or 4,342 mg/m^3). Ethylbenzene did not cause embryo toxicity, fetotoxicity or teratogenicity in rabbits at either exposure level. There were also no significant incidences of malformations or anomalies in foetal rabbits from either group, nor were any histological effects noted upon necropsy. There was no evidence of maternal toxicity in rabbits. The main observation noted by the investigators was a reduced number of live rabbit kits per litter, which occurred at both exposure levels. The number of implantations per litter and the number of dead or resorbed foetuses per litter were not significantly different from controls. The results of the rabbit study suggest a NOAEL of 100 ppm. The human equivalent NOAEL is 434 mg/m^3 (U.S. EPA, 1991). In the rats, both absolute and relative liver, kidney and spleen weights were significantly increased in pregnant rats from the 1,000 ppm group; however, there were no histopathological signs of maternal toxicity. There were also no effects observed on fertility or other measures of reproductive status. The principal observation was an increased incidence of supernumerary and rudimentary ribs in foetuses of the high exposure group and an elevated incidence of extra ribs in both exposure groups. However, this effect is considered to be non-teratogenic, as it is commonly observed with chemicals that cause maternal toxicity (Khera, 1984; Manson and Kang, 1989).

This same study also exposed groups of female rats to the same concentrations of ethylbenzene for three weeks prior to mating. Exposure was continued during gestation. As in the 1,000 ppm

group exposed during gestation only, there was an increased incidence of extra ribs in the high exposure group. However, an increased incidence of extra ribs was not seen at 100 ppm in these rats. There was no increase in rudimentary ribs in either exposure group. The apparent discrepancy in the incidence of extra ribs between the pregestationally-exposed group and those exposed only during gestation may be due to the fewer numbers of litters examined in the pregestationally-exposed group. No effects on fertility or any other measure of reproductive status were reported. No foetal toxicity was noted at either exposure level. Absolute and relative liver, kidney and spleen weights were significantly increased in pregnant rats in the 1,000 ppm group, but there were no histopathological effects noted in these organs. Skeletal variants were seen at both exposure levels, but were mild and considered marginally adverse. A LOAEL of 1,000 ppm (4,342 mg/m^3) was determined from this study.

Degeneration of the testicular epithelium was noted in guinea pigs and a rhesus monkey exposed to 600 ppm (2,604 mg/m^3) for six months (Wolf *et al.*, 1956). No effects were reported for female monkeys exposed to the same conditions.

4.1.5 Genotoxicity and Mutagenicity

One study was identified which evaluated genotoxic effects in humans after inhalation exposure to a mixture of chemicals, including ethylbenzene. Holz *et al.* (1995) studied low-level exposure to ethylbenzene and its effect on peripheral lymphocytes in workers at a styrene production plant. Twenty-five exposed workers were compared with 25 non-exposed controls working at the same company. The exposure groups were further stratified by smoking status. For the exposed group, air concentrations of ethylbenzene were reported to range from 365 to 2,340 mg/m^3 (84 to 539 ppm). However, measurements at one location (pump house) showed ethylbenzene concentrations exceeding 4,000 mg/m^3 (921 ppm). In the control group, ethylbenzene air concentrations were considerably lower and ranged from 145 to 290 mg/m^3 (33 to 67 ppm). No exposure-related genotoxic effects were detected by DNA adduct formation, DNA single strand breaks or sister chromatid exchanges. Increased numbers of kinetochore positive micronuclei in peripheral lymphocytes were observed in the total exposed group, and were also observed in exposed smokers and exposed non-smokers. However, the frequency of total micronuclei in peripheral lymphocytes was not significantly elevated. Interpretation of this study is limited by concurrent exposures of exposed workers to other chemicals including styrene, benzene, toluene and xylenes. The fact that controls were also exposed to ethylbenzene, albeit at lower concentrations than the exposed group, further confounds the results. The sample size in this study was also very small.

Ethylbenzene has been shown to be non-mutagenic in *Salmonella* strains TA98, TA1535, TA1537 and TA1538, and *Escherichia coli* strains WP2 and WP2uvrA, with or without metabolic activation (Nestmann *et al.*, 1980; Dean *et al.*, 1985). Ethylbenzene was shown to increase the mean number of sister chromatid exchanges in a human whole blood lymphocyte culture at the highest dose examined without metabolic activation (Norppa and Vainio, 1983). Ethylbenzene was negative in the *S. cerevisiae* JD1 gene conversion assay (Dean *et al.*, 1985).

NTP (1999) reported that ethylbenzene did not induce mutations in *Salmonella typhimurium* strain TA97, TA98, TA100 or TA1535, with or without S9 metabolic activation. In addition, no increases in sister chromatid exchanges or chromosomal aberrations were observed in cultured

Chinese hamster ovary cells treated with ethylbenzene, with or without S9. In the mouse lymphoma assay, a significant mutagenic response was noted in the absence of S9, but this only occurred at the highest nonlethal dose tested and was associated with cytotoxicity (NTP, 1999). The test was not performed with S9. NTP (1999) also reported no increases in the frequency of micronucleated erythrocytes *in vivo* in peripheral blood samples from male and female mice exposed to ethylbenzene for 13 weeks.

While the weight of available evidence strongly suggests that ethylbenzene is not mutagenic in most test systems, there is some limited evidence (*i.e.*, Holz *et al.*, 1995; NTP, 1999 – mouse lymphoma assay) that suggests potential genotoxic or mutagenic effects (ATSDR, 1999).

4.1.6 Carcinogenicity

No association has been found between the occurrence of cancer in humans and occupational exposure to ethylbenzene (ATSDR, 1999).

NTP (1999) exposed groups of 50 male and female F344/N rats to 0, 75, 250 or 750 ppm (0, 326, 1,088 or 3,263 mg/m^3) ethylbenzene by inhalation, six hours per day, five days per week, for 104 weeks. In male rats exposed to 750 ppm, the incidences of renal tubule adenoma and adenoma or carcinoma (combined) were significantly increased relative to controls. An extended evaluation (step section) of the kidneys showed a significant increase in the incidences of renal tubule adenoma and hyperplasia in males and females of the 750 ppm group, and the incidence of renal tubule adenoma or carcinoma (combined) was significantly increased in 750 ppm males. The incidence of interstitial cell adenoma in the testis of 750 ppm males was significantly greater than that in controls and was found to slightly exceed the historical control range for F344 rats in inhalation studies. NTP (1999) also exposed groups of 50 male and female B6C3F$_1$ mice to 0, 75, 250 or 750 ppm ethylbenzene by inhalation, six hours per day, five days per week, for 103 weeks. In 750 ppm males, the incidences of alveolar/ bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly increased relative to controls, but were within the NTP historical control ranges for this strain of mouse. In females of the 750 ppm group, the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly greater than those in the control group, but were also within the historical control ranges.

From these studies, the NTP concluded that there was "clear evidence of carcinogenic activity" of ethylbenzene in male F344/N rats based on increased incidences of renal tubule neoplasms, as well as increased incidence of testicular adenoma. There was "some evidence of carcinogenic activity" of ethylbenzene in female F344/N rats based on increased incidences of renal tubule adenomas. There was "some evidence of carcinogenic activity of ethylbenzene in male B6C3F$_1$ mice based on increased incidences of alveolar/bronchiolar neoplasms. There was "some evidence of carcinogenic activity" of ethylbenzene in female B6C3F$_1$ mice based on increased incidences of hepatocellular neoplasms. As defined by the NTP, clear evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related increase of (i) malignant neoplasms, (ii) combination of malignant and benign neoplasms, or (iii) benign neoplasms if there is an indication from this or other studies of the ability of such tumours to progress to malignancy. Some evidence of carcinogenic activity is defined as being demonstrated by studies that show a dose-related increase in the incidence of neoplasms

(malignant, benign or combined) for which the strength of the response is less than that required for "clear evidence".

Hard (2002) conducted a detailed review of the renal tumour and related renal effects data from the NTP (1999) study. A close association was noted between atypical tubule hyperplasia (ATH) and renal tumours, and chronic progressive nephropathy (CPN; an age-related spontaneous disease involving both degenerative and regenerative components) in the high dose groups. Based on this close association of ATH and renal tumours with CPN, it was concluded that the underlying mode of action for the renal tumours in this study was chemically induced exacerbation of CPN. Furthermore, this review concluded that this particular mode of action is not relevant for humans. Thus, the renal tumours observed in the NTP (1999) study should not be extrapolated to humans.

Potential factors underlying the carcinogenic mode of action of ethylbenzene in rats and mice of the NTP (1999) study were further evaluated by Stott *et al. (*2003). In male rats, kidney weight increases were accompanied by focal increases in hyaline droplets, alpha2u-globulin, degeneration and S-phase synthesis in proximal tubules. In the female rats, only decreased S-phase synthesis and MFO activities occurred. In mice, increased liver weights were accompanied by hepatocellular hypertrophy, mitotic figures, S-phase synthesis and enzyme activities. In addition, S-phase synthesis rates in terminal bronchiolar epithelium were elevated and showed a loss of MFO activity. The authors considered that these data, in combination with the general lack of genotoxic effects of ethylbenzene, suggest a mode of tumorigenesis that is dependent upon increased cell proliferation and altered cell population dynamics in male rat kidney and mouse liver and lungs.

Few regulatory agencies have classified ethylbenzene as to its carcinogenicity. The U.S. EPA categorizes ethylbenzene as "D - not classifiable as to human carcinogenicity", based on a lack of appropriate animal bioassays and human studies. The International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP) have not yet classified ethylbenzene for carcinogenicity. However, based on the findings of the NTP (1999) study, this may change in the near future. Similarly ethylbenzene is presently being reassessed under the IRIS program (U.S. EPA, 2003). Health Canada has not classified ethylbenzene with respect to its carcinogenic status.

4.2 Effects on Ecological Receptors

Aquatic Life

In freshwater fish, acute 96 hour LC50 values range from 4.2 mg/L in rainbow trout (*Oncorhyncus mykiss*) to 210 mg/L in channel catfish (*Ictalurus punctatus*) (Galassi *et al*., 1988; Johnson and Finley, 1980). LeBlanc (1980) reported a 48-hour EC50 and 24-hour LC50 in *Daphnia magna* of 1.8 mg/L and 77 mg/L, respectively. A number of studies with freshwater aquatic plants have reported toxicity thresholds that range from 4.6 to 4.8 mg/L (Herman *et al*., 1990).

In marine organisms, 24- to 96-hour LC50 values are reported to range from 4.3 mg/L in striped bass (*Morone saxatilis*) to 360 mg/L in sheepshead minnows (*Cyprinodon variegatus*)

(Heitmuller *et al.*, 1981). In marine pelagic invertebrates, 24- to 48-hour LC50 values are reported to range from 0.49 mg/L in bay shrimp (*Crago franciscorum*) to 5.2 mg/L in mysid shrimp (*Mysidopsis bahia*) (Masten *et al.*, 1994).

Invertebrates

In the collembolan, *Onychiurus folsomi*, LC25 values for ethylbenzene in coarse and fine soils were 576 mg/kg and 259 mg/kg, respectively (ESG, 2002; Komex, 2002). In the earthworm, *Eisenia andrei*, NOEC and LOEC values for ethylbenzene were 16 and 112 mg/kg in coarse soil (ESG, 2002). The geometric mean of the NOEC and LOEC values in fine soil was reported to be 42 mg/kg (Komex, 2002).

Plants

ESG (2002) conducted 14 day plant toxicity tests with ethylbenzene using Northern wheatgrass (*Agropyron dasystachyum*) and alfalfa (*Medicago sativa*) in coarse and fine soils. In coarse soils, an IC25 of 462 mg/kg was reported for alfalfa, based on a reduction in root length. An IC25 of 3 mg/kg was reported for wheatgrass based on reduced root wet mass. In fine soils, the IC25 values were 316 mg/kg for alfalfa (reduced root length) and 218 mg/kg for wheatgrass (reduced root wet mass) (ESG, 2002; Komex, 2002).

Other Environmental Effects

Based on the available data on the environmental fate, transport and effects of ethylbenzene, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns. The photooxidation of ethylbenzene could produce such products as peroxyacetyl nitrate, ethylphenol, benzaldehyde, acetophenone and ethylnitrobenzenes, and may contribute to the formation of photochemical smog in the atmosphere (WHO, 1996). One particular by-product of ethylbenzene photodegradation is peroxyacetyl nitrate (PAN), which is a known irritant component of photochemical smog. However, ethylbenzene has a relatively low smog formation potential relative to alkenes, as it is less photochemically reactive (ATSDR, 1999). Yanagihara *et al.* (1977) report that its photoreactivity is intermediate to other volatile organic compounds.

Summary

In humans, the symptoms of acute ethylbenzene intoxication following inhalation exposure include: respiratory tract and ocular irritation, chest constriction, a burning sensation, dizziness, vertigo and minor hematological changes. Symptoms of acute ethylbenzene toxicity in experimental animals are similar to those observed in humans in that eye and respiratory tract irritation is frequently reported, but acute toxicity in animals is also manifested by neurological and neurobehavioral effects, impaired hearing, altered liver and kidney enzyme levels and increased liver weights. Subchronic and chronic inhalation exposure to ethylbenzene results primarily in kidney and liver effects in experimental animals. Developmental studies have reported minor effects of ethylbenzene including extra ribs and skeletal variants, with maternal toxicity occurring at lower doses than developmental toxicity. The carcinogenicity evidence for ethylbenzene is equivocal. While the NTP (1999) study indicated evidence of carcinogenic

effects in rats and mice, a recent review of the histopathological effects in this study indicates that the observed renal tumour types should not be extrapolated to humans (Hard, 2002). The weight of available evidence from genotoxicity and mutagenicity studies strongly suggests that ethylbenzene is not mutagenic in most test systems.

Based on a review of current and/or ongoing research and/or assessment activities or programs overseen by Health Canada, Environment Canada, Canadian Council of Ministers of the Environment (CCME), U.S. National Toxicology Program (NTP), U.S. National Institute of Health CRISP Database, U.S. National Institutes of Environmental Health Sciences (NIEHS), various U.S. EPA offices and programs (*e.g.*, TSCA, Science Advisory Board reports, etc.), Chemical Industries Institute of Toxicology (CIIT), Toxicology Excellence for Risk Assessment (TERA), World Health Organization (WHO), Agency for Toxic Substances and Disease Registry (ATSDR) and Health Effects Institute (HEI), there appear to be few current or ongoing studies or reviews specifically related to ethylbenzene toxicology under the direction of these agencies and institutes. The toxicological significance of the metabolism of alkylbenzenes (which includes ethylbenzene) is currently being investigated by W.L. Backes (Louisiana State University). The objective of this project is to supply information that will aid in the identification of conditions under which individuals might be susceptible to alkylbenzene (including ethylbenzene) toxicity. Ethylbenzene is presently being reassessed under the IRIS program (U.S. EPA, 2003).

5.0 AMBIENT MONITORING METHODS

This section assesses the various air monitoring methodologies to measure ethylbenzene in ambient air and describes their advantages and disadvantages.

5.1 Background

5.1.1 Introduction

Air monitoring is used to determine the concentrations of chemical species in the atmosphere. For any single chemical species, there are typically several methods that can be used, with varying detection levels, sampling periods/frequencies and operational levels-of-effort. Specific air monitoring methods include continuous, integrated passive, grab sampling and integrated active (Lodge, 1988). Many factors must be considered in selecting the best approach based on the overall objectives of the monitoring program. Considerations include minimum detection levels, measurement precision, averaging period and cost.

5.1.2 General Monitoring Approaches

In continuous monitors, a sample of air is drawn past a fast response detector using a pump. The detector produces an electrical signal that is proportional to the concentration of a specific chemical compound. Hourly average concentration information can be recorded by a digital data collection system (*i.e.*, a computer) or other storage medium (chart recorder).

In integrated passive sampling, a reactive surface in a controlled diffusion path is exposed for a nominal period ranging from 24 hours to one-month. The reactive surface is analyzed in a chemical laboratory to determine the concentration of the captured compounds. The method is termed passive because pumps are not drawing an air sample past a detector or through a collection medium.

In grab sampling, a whole air sample is collected in a non-reactive steel canister or plastic bag. The air sample is then analyzed in a laboratory to determine the concentration of the compounds in the air sample. Grab samples typically represent samples collected over the course of a few minutes to several hours.

In integrated active sampling, a known volume of air is drawn through a column filled with an absorbent material (for gases) or a collection filter (for particles) using a pump. These absorbent columns or filters are then analyzed in a laboratory to determine the concentrations of the collected compounds. Integrated samples are typically collected once every six days for a 24-hour period.

Integrated samplers require a sorbent to entrap the chemical species being sampled. The selection of the sorbent will depend on the specific compounds being sampled. Commonly used sorbents include, but are not limited to, Tenax, XAD-2, activated charcoal, Carbotrap C, Anasorb 747, Carbosieve, or a multi-stage combination using more than one sorbent. Dewulf and Langenhove (1997) describe four criteria that can be used in the selection of an appropriate sorbent. Firstly, it is important that the sampled compounds to not breakthrough the sorbent and

that the specific retention volume of the sorbent is known. Secondly, the sorbent cannot influence the sample by causing unwanted reactions with the sample. Thirdly, it is imperative that the sorbent not be contaminated prior to and after the sampling process. And lastly the retention of water on the sorbent should be small to avoid any interference with the laboratory analysis of the sample.

5.1.3 Laboratory Analysis

Collected samples (grab sampling) or sample media (integrated sampling) are analyzed to determine the respective concentrations. The most common process uses a gas chromatograph (GC) coupled to an appropriate detector. The GC process requires the sample to be placed in a heated chamber and purged with inert gas (*e.g.* helium) to separate and transfer the VOC sample from the sorbent, through a cold trap, onto the front of the GC column, which is initially at a low temperature. The GC column is heated to elute individual compounds based on their retention time (Lodge, 1988). The GC is usually coupled to an appropriate detector. Based on the required specificity and sensitivity of the application, there are several specific and non-specific detectors that can be used.

Non-specific detectors include the nitrogen-phosphorous detector (NPD), the flame ionization detector (FID), the electron capture detector (ECD) and the photo-ionization detector (PID) (U.S. EPA, 1999a). These detectors are generally less costly per analysis than specific detectors and can be more sensitive for specific classes of compounds. For example, if multiple halogenated compounds are targeted, using the ECD would provide more accurate identification. The non-specific detectors are coupled to the GC and individual compounds are identified by their retention time. The downside of using non-specific detectors is that they are prone to greater margins of error since they rely on retention times alone for compound identification. Also, there is a chance that interference can occur due to non-targeted compounds (U.S. EPA, 1999a).

Specific detectors include the linear quadrupole mass spectrometer (MS) and the ion trap detector. Both of these detectors are mass spectrometers. The mass spectra for individual peaks in the ion chromatogram are analyzed for the fragmented mass patterns of the primary and secondary ions. These fragmentations are compared to known spectra observed under like conditions. Based on the GC retention time and the mass spectral characteristics, each VOC in the sample can be determined.

Mass spectrometry is a more accurate method of determining specific compounds in ambient air samples because of their range of precision and simple identification process. Although the non-specific detectors have some advantages such as lower cost and higher sensitivity, the U.S. EPA (1999b) stresses that mass spectrometry is considered a more definitive identification technique and reduces the chances of misidentification.

5.1.4 Information Sources

Standardized air monitoring methods are documented by the U.S. Environmental Protection Agency (U.S. EPA), the Occupational Safety and Health Administration (OSHA) and the National Institute of Occupational Safety and Health (NIOSH). These agencies provide detailed approaches required to adequately measure hazardous air pollutants (HAPs) in ambient and

workplace air using a variety of air monitors and analysis techniques. Other information sources (*e.g.* technical journals, conference proceedings) were also reviewed to explore other air monitoring technologies, as well as new or emerging technologies.

5.1.4.1 U.S. EPA

The U.S. EPA has developed several air toxics methodologies for sampling VOC in ambient air. Detailed descriptions of these methods are available on the U.S. EPA Technology Transfer Network (TTN) – Ambient Monitoring Technology Information Center (AMTIC). The following U.S. EPA air toxics methods can be used to sample ethylbenzene:

- Compendium Method TO-1: Method for the determination of volatile organic compounds in ambient air using Tenax adsorption and gas chromatography/mass spectrometry (GC/MS) (U.S. EPA, 1984).
- Compendium Method TO-14A: Determination of volatile organic compounds in ambient air using specially prepared canisters with subsequent analysis by gas chromatography (GC) (U.S. EPA, 1999a).
- Compendium Method TO-15A: Determination of volatile organic compounds in air collected in specially prepared canisters and analyzed by gas chromatography/mass spectrometry (GC/MS) (U.S. EPA, 1999b).
- Compendium Method TO-17: Determination of volatile organic compounds in ambient air using active sampling onto sorbent tubes (U.S. EPA, 1999c).

Each of these methodologies can be applied to a range of VOC as determined by previously successful trials conducted by the U.S. EPA. All four methods can be used to sample and analyze ethylbenzene. The following sections describe each U.S. EPA method.

U.S. EPA Compendium Method TO-1

Method TO-1 is limited to non-polar organic compounds that have a boiling point between 80° and 200°C. The U.S. EPA provides a list of compounds that can be sampled using this method as not all non-polar organic compounds within that boiling range can be determined. Ethylbenzene is among those compounds that can be determined.

This method uses sorbent tubes to trap VOC in ambient air. The ambient air to be sampled is drawn through a chamber containing Tenax (poly 2,6-Diphenyl phenylene oxide) sorbent. The ethylbenzene adheres to the Tenax sorbent while other highly volatile organic compounds and most inorganic components pass through the chamber. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Compendium Method TO-14A

Method TO-14A provides procedures for sampling VOC in pressurized (above atmospheric pressure) and subatmospheric pressure (below atmospheric pressure) canisters. Originally, this method was based on the collection of whole ambient samples using SUMMA passivated stainless steel canisters but can now be applied to other types of canisters. It can be applied to ambient concentrations of VOC above 0.5 ppbv and will usually require a sample size on the

order of one litre. The U.S. EPA provides a list of compounds that can be sampled based on their storage capability in canisters. Ethylbenzene is among those compounds that can be determined.

This method uses an empty canister and pump-ventilated sample line for sample collection. For pressurized sampling, an additional pump to pressurize the canister is required. The ambient air sample is drawn through a sampling train, which is made up of components that regulate the rate and length of sampling, into the specially prepared passivated canister. The sample is transferred to a laboratory for analysis with a GC coupled to one of many GC detectors described in Section 5.1.4.

U.S. EPA Compendium Method TO-15A

Method TO-15A is an extension of the sampling method TO-14A. This method is more generalized but provides better definitions for VOC sampling methods. The set of compounds that can be sampled using the specially prepared canisters is a subset of the 97 VOCs that are listed as hazardous air pollutants in the 1990 amendments of the U.S. Clean Air Act, and includes ethylbenzene. This list includes more compounds than are described in Method TO-14A. The only means of laboratory analysis for this method is by GC/MS. Further, Method TO-15A includes more detailed guidelines for quality control, mainly internal analytical standards and frequent verification of analytical performance.

U.S. EPA Compendium Method TO-17

Method TO-17 is a thermal desorption based ambient air monitoring method for VOC and is applicable for 0.5 and 0.25 ppbv ambient concentration levels. The U.S. EPA provides a list of compounds for which this method can be used based on sampling performance. These compounds, which are the same as those that can be sampled using TO-15A, are a subset of the 97 VOCs that are listed as hazardous air pollutants in the 1990 amendments of the U.S. Clean Air Act. Ethylbenzene is among those compounds that can be determined.

This method uses single or multi sorbents packed in tubes in order of increasing sorbent strength, allowing for a wide volatility range of VOC to be sampled. Using multi-sorbent tubes, compounds with higher molecular weights are retained first and compounds with lower molecular weights last. If a single sorbent is being used, it should be specific to the target compound. Because of the specificity of certain sorbents, the thermal desorption process is very efficient.

The sample is drawn through a tube containing the selected sorbents. The ethylbenzene adsorbs to the sorbents while unwanted VOC and most other inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

5.1.4.2 NIOSH

NIOSH has developed several air toxics methodologies for sampling VOC in workplace air. Detailed descriptions of these methods are contained in the NIOSH Manual of Analytical Methods (NMAM). It should be noted that the NMAM was intended to achieve consistent

industrial hygiene analyses and was not designed specifically for ambient air. The following NIOSH analytical method can be used to sample ethylbenzene:

- NIOSH Manual of Analytical Methods, Fourth Edition, Method 1501: Hydrocarbons, Aromatic (NIOSH, 1994).

According to NMAM, Method 1501 is the only method that can be used to sample and analyze ethylbenzene. The following section describes method 1501 in detail.

NIOSH Method 1501

Method 1501 employs an activated charcoal based solid sorbent tube similar to that described in U.S. EPA Compendium Method TO-17. This method is limited to the activated charcoal (prepared from coconut shells) sorbent, which is a commonly used sorbent because of its reactive surface which promotes higher adsorptive capacity. Also, it has a very high area to weight ratio, which allows for higher sampling capacity.

The sample is drawn through a tube containing the activated charcoal sorbent. The ethylbenzene would adsorb to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

5.1.4.3 OSHA

OSHA has developed several air toxics methodologies for sampling VOCs in ambient air. Detailed descriptions of these methods are available from the Directorate of Science, Technology and Medicine (DSTM): Salt Lake Technical Center (SLTC). It should be noted that these methods were intended to provide a uniform and practical means for evaluating workplace air quality and were not designed specifically for ambient air. The following OSHA analytical methods can be used to sample ethylbenzene:

- OSHA Sampling and Analytical Methods, Organic Method 7: Organic Vapours (OSHA, 2000).
- OSHA Sampling and Analytical Methods, Organic Method 1002: Xylene (o-, m-, p-isomers) and Ethylbenzene (OSHA, 1999).

Organic Method 7 can be applied to a range of organic compounds whereas organic Method 1002 is limited to xylene (o-, m-, p-isomers) and ethylbenzene. Organic Method 7 is a very general sampling method and provides a list of compounds that can be determined. Unlike other sampling methodologies, OSHA usually provides methods for individual and grouped compounds. For example, Method 1002 describes all the possible sampling methods that can be used for xylene and ethylbenzene. The following sections describe both OSHA methods.

OSHA Method 7

Method 7 is a general organic vapour sampling methodology. It uses an activated charcoal based solid sorbent tube similar to that described in NIOSH Method 1501. Activated charcoal

(prepared from coconut shells) is a commonly used sorbent because its reactive surface promotes higher adsorptive capacity. Also, it has a very high area to weight ratio, which allows for higher sampling capacity.

The sample is drawn through a tube containing activated charcoal sorbent. The ethylbenzene adsorbs to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

OSHA Method 1002

Method 1002 is limited to xylene (o-, m-, p-isomers) and ethylbenzene only. There are two possible ways to sample ethylbenzene as described in this method. The first method is the same as Method 7; using an activated charcoal sorbent as the collection medium. A second method for ethylbenzene is diffusive sampling. This is a passive sampling technique using the SKC 575-002 passive sampler.

The SKC 575-002 passive sampler is a very small sampler that can be affixed to a worker's collar. Since OSHA is primarily interested with workplace safety, they suggest that the monitor should be placed near the breathing area (*i.e.* mouth and nose). The air to be sampled is drawn through a mesh screen and through the desorption solvent chamber. The sorbent used by this sampler is called Anasorb 747 and is a synthetic carbon which can be used for a larger array of compounds than the coconut charcoal used in the sorbent tubes described in OSHA method 7. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

5.1.4.4 Alternative and Emerging Technologies

The combination of the U.S. EPA, NIOSH and OSHA ambient air sampling methods provides a broad scope of approaches. The sampling methods described in this section are designed for use over an 8-h to 24-h period. There are, however, other notable methods of sampling ethylbenzene that have been used in the past for specific applications.

Kuo *et al.* (2000) sampled the roadside concentrations of certain VOC including ethylbenzene in Taichung, Taiwan. Their methodology was a similar approach as U.S. EPA Compendium TO-17, NIOSH method 1501 and OSHA method 7. A small stainless steel tube containing a Carbopack B sorbent and a low-flow sampling pump was attached to the collar of motorists. A GC coupled to a MS was used for analysis of samples.
Uchiyama et al. (1999) successfully used a modified diffusion sampler with thermal desorption for analysis since higher sensitivity was required for their application. The diffusive sampler used either Carboxen or Carbotrap B sorbents to collect VOC through the molecular diffusion and collection. A GC coupled to a MS was used for analysis of samples.

Leibrock and Slemr (1997) conducted a fairly unique, yet effective, sampling technique without the use of a sorbent. Their sampler design employed two cryogenic sampling traps that would remove compounds from the ambient air being drawn into the sampler dependant on their temperature resistance. A GC coupled to a MS was used for analysis of samples.

Environment Canada has used SUMMA canisters based on the U.S. EPA Compendium TO-14A to measure for urban pollutants. This method has also been used in Edmonton, Alberta (Cheng *et al.*, 1997) to measure the concentration of VOC (including ethylbenzene) in ambient air.

For long-term exposure trends, passive diffusion monitors such 3M 3500 Organic Vapour Monitors have been used. Usually these monitors are exposed for seven to 24 days and returned to a laboratory for analysis. In a recent animal health study, these monitors were used to measure VOC concentrations in rural Alberta, Saskatchewan and British Columbia.

As new and emerging technologies are developed, agencies such as the U.S. EPA provide information to users ensuring that the best available environmental practices are upheld.

6.0 EXISTING AMBIENT GUIDELINES

Current recommended or proposed ethylbenzene ambient air quality guidelines from selected regulatory agencies in Canada (other than Alberta), the United States and elsewhere are summarized in Table 9. Appendix A contains further information on each of these existing guideline values.

In general, all jurisdictions reviewed have common uses for their ambient air quality guidelines, including:

- Reviewing permit applications for air emission sources;
- Investigating accidental releases or community complaints about adverse air quality for the purpose of determining follow-up or enforcement activity;
- Conducting health risk assessments of industrial facilities and airsheds; and
- Monitoring and controlling ambient air quality.

The development of ambient air quality guidelines is driven by numerous societal and scientific issues, which require consideration of numerous factors such as aesthetics, property damage, toxicology and ecology. Odour, for example, is an issue of aesthetics, and for chemicals with particularly distasteful odours, guideline values may be driven by odour thresholds, while for airborne chemicals that are corrosive, damage to structures may be a key consideration.

In terms of toxicology, air quality guidelines typically consider basic toxicological principles, which dictate that the response of an organism is a function of the magnitude of the dose and the duration over which the dose is received. The nature of the response of organisms (*i.e.*, the target tissues or organs and the toxicological endpoints) is another important consideration. For example, chemicals that act as primary respiratory irritants may have guidelines developed that are protective of these types of effects. Where toxicity concerns relate to non-respiratory targets (*e.g.*, liver or kidney) or to toxicological endpoints of late onset (*e.g.*, cancer, reproductive), air quality guidelines may be established to be protective of these types of effects. Chemicals that have multiple toxicological endpoints in more than one tissue or organ may have guidelines developed that are protective of the most sensitive toxic effects. Another consideration is the estimated or actual degree of exposure of key receptors to the air pollutant, particularly receptor groups that may exhibit sensitivity to the air pollutant (*e.g.*, elderly, asthmatics, children, *etc.*). Other important considerations in establishing an air quality guideline include the available technologies (and their costs) for routinely or periodically monitoring for the pollutant in air, and the availability and technical feasibility of approaches for estimating ambient ground-level air concentrations, in order to compare to air quality guidelines.

The three most common approaches by which ambient air quality guidelines are developed are as follows:

1. Using an occupational exposure level (OEL) and dividing it by safety or uncertainty factor, and amortizing for continuous exposure. These factors are intended to account for differences between 8-hour exposures in the workplace and continuous 24-hour environmental exposures, increased susceptibility of individuals in the general population

versus the relatively healthy worker, and uncertainties in the margin of safety provided in an occupational exposure limit. It should be recognized however, that the use of OEL values has its limitations. For example:

- OELs are based on human effects information in industrial settings and may not accurately reflect ambient environmental exposure situations.
- OELs are derived to be protective of workers who are typically considered in good health and within the age range of 18 to 65 years. Such individuals are potentially less sensitive and/or susceptible to the effects of airborne pollutants than members of the general population. Among the general populations, there may be subpopulations or individuals that are more sensitive or susceptible to the effects of an airborne pollutant (*e.g.*, elderly, young children, asthmatics, people with pre-existing respiratory conditions, etc.)
- Worker exposures are typically based on a normal work schedule (eight hours per day, five days per week). For this work schedule, there are two days per week (weekends) in which the body may eliminate much of the accumulated substances before the next workweek begins. However, for individuals continuously exposed to an air pollutant in the ambient environment, there is no similar period of no exposure.
- For these reasons, agencies using OELs as the basis for ambient air quality guidelines typically adjust OELs by applying safety or uncertainty factors.

2. Threshold chemical risk assessment procedures: Used for chemicals that are not believed to act as carcinogens and that exhibit a clear toxicity threshold. In this approach, a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) from a suitable animal or human study is divided by a series of uncertainty factors that account for issues such as: differences between animals and humans, sensitive individuals, use of a LOAEL instead of a NOAEL, and for extrapolation from subchronic to chronic exposure durations.

3. Non-threshold chemical risk assessment procedures: Used for substances believed act as carcinogens. Cancer potency estimates, slope factors, tumorigenic potency values, etc. are used to establish ambient air levels based on acceptable levels of incremental lifetime cancer risk, such as one in 100,000. These acceptable levels are established by regulatory agencies.

Finally, the potential ecological impacts of airborne chemicals are also important considerations in the guideline-setting process. Although a chemical may have no direct impact on human health or property, transfer of the chemical from the air to the terrestrial and aquatic environments by dry or wet deposition could have ecological impacts, depending on the physical and chemical properties of the substance.

Current occupational exposure limits for ethylbenzene derived by ACGIH, NIOSH and OSHA are all based on human studies where irritant effects were demonstrated at air concentrations above 100 ppm (435 mg/m^3). These agencies all consider ethylbenzene to be of low toxicity by any route and the airborne concentration limits are intended to prevent "disagreeable irritation". The current ACGIH TLV-TWA, OSHA PEL-TWA and NIOSH REL values are all 100 ppm (435 mg/m^3). OSHA (1989) concluded that workers exposed to concentrations of ethylbenzene above 100 ppm, even for brief periods, have a significant risk of experiencing irritation. Short-

term or ceiling exposure levels have also been established for ethylbenzene by these agencies. The current STEL values from ACGIH, OSHA and NIOSH are all 125 ppm (544 mg/m^3). ACGIH (1991) reports that occupational exposure limits from other countries are similar. For example, Australia, Germany and the United Kingdom (U.K.) use a threshold value of 100 ppm (435 mg/m^3). Australia and the U.K. use a 10-minute STEL of 125 ppm (544 mg/m^3). Germany uses a short-term level of 200 ppm (870 mg/m^3). Sweden uses an occupational limit of 80 ppm (348 mg/m^3) and a 15-minute short-term value of 100 ppm (435 mg/m^3).

NIOSH (2003) reports an immediately-dangerous-to-life-and-health (IDLH) value of 800 ppm (3,480 mg/m^3). The IDLH is based strictly on safety considerations and is 10% of the lower explosive limit of 0.8%. Thus, it does not represent an appropriate basis for establishing an ambient air quality guideline.

The U.S. EPA, ATSDR and CalEPA OEHHA have derived health-based airborne ambient exposure levels for ethylbenzene.

The OEHHA (2003) chronic REL of 2.0 mg/m^3 is based on the chronic rat and mouse NTP (1999) study. The NOAEL for non-neoplastic effects (nephrotoxicity, liver changes, pituitary gland hyperplasia and body weight changes) in this study was 75 ppm (326 mg/m^3) and the LOAEL was 250 ppm (1,088 mg/m^3). This study is the most recent available and was considered the most reliable for assessing chronic effects of ethylbenzene exposure. OEHHA calculated the human-equivalent concentration of the NOAEL to be 13 ppm (56.6 mg/m^3). A cumulative uncertainty factor of 30 was applied to the NOAEL of 13 ppm [3-fold for interspecies differences; 10-fold for intraspecies differences] to yield the chronic REL. The OEHHA compared the chronic REL value of 0.4 ppm to potential developmental REL values that were calculated based on the studies by Andrew *et al.* (1981), Hardin *et al.* (1981) and Ungvary and Tatrai (1985) and found that there is a sufficient margin of safety in the current REL to provide protection against the reported developmental effects of ethylbenzene. The OEHHA has not derived an acute REL for ethylbenzene.

The current U.S. EPA (1991) RfC of 1.0 mg/m^3 was derived from the developmental toxicity studies in rats and rabbits conducted by Andrew *et al.* (1981) and Hardin *et al.* (1981). A NOAEL of 100 ppm (434 mg/m^3) was reported in these studies. The U.S. EPA applied an uncertainty factor of 300 and a modifying factor of one to this NOAEL to yield the RfC. The uncertainty factor of 300 reflects a factor of 10 to protect unusually sensitive individuals, 3 to adjust for interspecies conversion and 10 to adjust for the absence of multigenerational reproductive and chronic studies. Overall confidence in this inhalation RfC is considered low by the U.S. EPA (U.S. EPA, 1991).

The ATSDR (1999) has derived an intermediate duration (14 to 364 days) Minimal Risk Level (MRL) for ethylbenzene, but has not developed an acute or chronic MRL at this time. The intermediate MRL is 1.0 ppm (4.34 mg/m^3) and was derived from a NOAEL of 97 ppm (422 mg/m^3) for developmental effects in Wistar rats reported by Andrew *et al.* (1981). This NOAEL was divided by an uncertainty factor of 100 (10-fold for extrapolation from animals to humans after adjusting for the human equivalent concentration, and 10-fold for human variability) to yield the MRL value.

For the most part, the guidelines presented below in Table 9 are derived based on either the U.S. EPA RfC of 1.0 mg/m^3, the studies by Andrew *et al.* (1981) and Hardin *et al.* (1981), or the ACGIH TLV-TWA or STEL values of 100 ppm (435 mg/m^3) or 125 ppm (544 mg/m^3), respectively (adjusted with various modifying and uncertainty factors). The TNRCC criteria differ from the other jurisdictions reviewed in that they are based upon odour effects of ethylbenzene, rather than health effects data. In the available documentation from some agencies, the basis behind the air quality guideline is not clearly specified. Further information on the scientific basis for these guidelines, the application of uncertainty factors and the practical application of these guidelines by the respective agencies, is provided in Appendix A.

Table 9 Summary of Existing Air Quality Guidelines for Ethylbenzene

Agency	Name of Guideline (Averaging Period)	Guideline Value (mg/m^3)	Basis of Guideline	Date of Guideline[a]
California Environmental Protection Agency, Office of Environmental Health Hazard Assessment	Chronic REL (continuous lifetime daily exposure)	2.0	NTP, 1999	2002
Louisiana Department of Environmental Quality	AAS (8 h)	10.3	Not provided in available documentation.	2003
Massachusetts Department of Environmental Protection	TEL (24 h) AAL (annual) ATC (continuous lifetime daily exposure)	0.3 0.3 1.5	U.S. EPA RfC of 1.0 mg/m^3	1995
Michigan Department of Environmental Quality	ITSL (24 h) IRSL (annual) SRSL (annual)	1.0 0.003 0.03	ITSL is based on U.S. EPA RfC of 1.0 mg/m^3. The IRSL and SRSL are not clearly specified in the available documentation, but are noted to be established by State toxicologists based on available inhalation toxicity data Rule 229 procedures.	1990 for ITSL; 2002 for IRSL and SRSL
Minnesota Department of Health	HRV (1 h)	10.0	Not clearly specified in the available documentation, but are noted to be derived using best peer-reviewed science and public health policies available.	2003
Netherlands Research for Man and Environment (RIVM)	TCA (continuous lifetime daily exposure)	0.77	Andrew *et al.*, 1981; Hardin *et al.*, 1981	2001
Newfoundland and Labrador Department of the Environment	AQS (1 h) POI (1 h)	4.0 3.3	Not provided in available documentation.	2003
New Hampshire	AAL (24 h)	1.0	Based on U.S. EPA RfC	1997

Agency	Name of Guideline (Averaging Period)	Guideline Value (mg/m^3)	Basis of Guideline	Date of Guideline[a]
Department of Environmental Services	AAL (annual)	1.0	of 1.0 mg/m^3	
New Jersey Department of Environmental Protection	Short term RfC (24 h)	1.0	Based on U.S. EPA RfC of 1.0 mg/m^3	2003
New York State Department of Environmental Conservation	SGC (1 h) AGC (continuous lifetime daily exposure)	54.0 1.0	The SGC is based on the ACGIH TLV STEL of 125 ppm. The AGC is based on the U.S. EPA RfC of 1.0 mg/m^3	2000
Oklahoma Department of Environmental Quality	MAAC (24 h)	43.4	Based on ACGIH TLV-TWA of 100 ppm.	2003
Ontario Ministry of Environment and Energy	AAQC (24 h) AAQC (10 min) POI (1/2 h)	1.0 1.9 3.0	24 h AAQC based on U.S. EPA RfC of 1.0 mg/m^3; 10 min AAQG based on odour threshold of 1.9 mg/m^3; POI based on three times the 24 h AAQG	2001
Quebec Ministry of the Environment	MAAQC (continuous lifetime daily exposure)	0.20	Based on U.S. EPA RfC of 1.0 mg/m^3	2002
Texas Natural Resource Conservation Commission	Short- term ESL (1 h) Long-term ESL (annual)	2.0 0.2	Based on odour nuisance potential	2003
U.S. Agency for Toxic Substances and Disease Registry	Intermediate MRL (14-364 days)	4.34	Andrew *et al.*, 1981	1999
U.S. Environmental Protection Agency, Integrated Risk Information System (IRIS)	RfC (continuous lifetime daily exposure)	1.0	Andrew *et al.*, 1981; Hardin *et al.*, 1981	1991 (IRIS database accessed November 2003)
Vermont Agency of Natural Resources	HAAS (8 h)	43.5	Based on ACGIH TLV-TWA of 100 ppm.	2001
Washington Department of Ecology	ASIL (24 h)	1.0	Based on U.S. EPA RfC of 1.0 mg/m^3	1998
World Health Organization	GV (annual)	22.0	Based on NOAEL of 2.15 mg/m^3 for increased organ weight. Study not specified in available documentation.	1999

a Date guideline was either promulgated or date of last review/revision by agency.

The air quality guideline values used by the jurisdictions listed in Table 9 can be split into short-term and long-term values. Short-term ambient air guidelines for ethylbenzene include 10-minute, half-hour, one-hour, eight-hour and 24-hour averaging periods. Ontario is the only jurisdiction with a 10-minute and a half-hour limit (1.9 and 3.0 mg/m^3, respectively). One-hour

limits exist in Minnesota, Newfoundland and Labrador, New York and Texas. The lowest one-hour guideline is 2.0 mg/m^3 (Texas), while the highest is 54.0 mg/m^3 (New York). Louisiana and Vermont cite eight-hour limits of 10.3 and 43.5 mg/m^3, respectively. Twenty-four hour guidelines exist in Massachusetts, Michigan, New Hampshire, New Jersey, Oklahoma, Ontario and Washington. These 24-hour guideline values range from 0.3 mg/m^3 (Massachusetts) to 43.4 mg/m^3 (Oklahoma). Long-term air quality guidelines in the jurisdictions reviewed are generally listed as annual ambient limits or are stipulated for continuous lifetime daily exposure. Annual limits exist within California, Massachusetts, Michigan, The Netherlands, New Hampshire, New York, Quebec, Texas, the U.S. EPA and the World Health Organization. These values range from 0.003 mg/m^3 (Michigan) to 22.0 mg/m^3 (World Health Organization). ATSDR developed an intermediate Minimal Risk Level of 4.34 mg/m^3 for a duration of 14 to 364 days.

It should be noted that the considerable variability observed between guidelines is primarily the result of differences in the approaches used in their derivation. While there is generally good agreement with respect to the choice of toxicological studies and data used as the basis for the guidelines, all jurisdictions use different averaging periods and apply unique sets of uncertainty and modifying factors and assumptions in guideline development. The decision to use a particular approach involves policy decisions in addition to scientific considerations.

7.0 DISCUSSION

Ethylbenzene is not corrosive. While it is highly flammable, this is a safety issue that is separate and distinct from health-based guideline development. The carcinogenicity evidence for ethylbenzene is equivocal. While the NTP (1999) study indicated evidence of carcinogenic effects in rats and mice, a recent review of the histopathological effects in this study indicates that the observed renal tumour types should not be extrapolated to humans (Hard, 2002). At present, few regulatory agencies have classified ethylbenzene as to its carcinogenicity. The U.S. EPA categorized ethylbenzene as "D - not classifiable as to human carcinogenicity", based on lack of appropriate animal bioassays and human studies. The International Agency for Research on Cancer (IARC), Health Canada and the National Toxicology Program (NTP) have not yet formally classified ethylbenzene as to its carcinogenicity. Furthermore, there are currently no existing ambient air quality guidelines or other health-based airborne exposure limits that are based on the carcinogenic effects reported in NTP (1999). The weight of available evidence from genotoxicity and mutagenicity studies strongly suggests that ethylbenzene is not mutagenic in most test systems, although there is some evidence that suggests potential genotoxic or mutagenic effects in human lymphocytes and in the mouse lymphoma assay (*i.e.*, Holz *et al.*, 1995; NTP, 1999; ATSDR, 1999). Based on these considerations, toxicological considerations for ethylbenzene should focus on non-cancer endpoints following acute and chronic exposure.

Review of the physical chemical properties (Section 2.0) and the toxicology (Section 4.0) of ethylbenzene indicate several key benchmark air concentrations that should be considered in establishing an ambient air quality guideline. First, odour thresholds for ethylbenzene are highly variable and have been reported to range from as low as 0.4 mg/m^3 to as high as 78.3 mg/m^3 (WHO, 1996; Verschueren, 1983; van Gemert, 1999; Amoore and Hautala, 1983; Cometto-Muniz and Cain, 1995).

The acute toxicity of ethylbenzene is characterized primarily by respiratory tract and ocular irritation, lacrimation (tearing), chest constriction, a burning sensation, dizziness, vertigo and minor hematological changes. A number of acute human and animal studies have demonstrated various adverse effects at concentrations above 300 ppm (1,305 mg/m^3). At air concentrations below 100 ppm (435 mg/m^3) there appear to no adverse effects, including a lack of irritation effects. All current occupational exposure limits for ethylbenzene derived by ACGIH, NIOSH and OSHA are based on human studies where irritant effects were demonstrated at air concentrations above 100 ppm (435 mg/m^3).

The available human epidemiology studies are inconclusive, suffer from a number of methodological and reporting limitations, and are confounded by concurrent exposures to other chemicals. Subchronic and chronic inhalation studies with ethylbenzene in experimental animals have demonstrated a variety of adverse effects. NTP (1992) reported a LOAEL of 1,000 ppm (4,350 mg/m^3) for organ weight changes. A NOAEL of 75 ppm (326 mg/m^3) was suggested by OEHHA (2003) from the NTP (1999) study based on a variety of non-neoplastic effects in rats and mice. The U.S. EPA (1991) identified NOAEL (HEC) values of 606 mg/m^3 in mice and rats, and 1,249 mg/m^3 in rabbits, from the Cragg *et al.* (1989) study. From the study by Elovaara *et al.* (1985), the U.S. EPA (1991) identified a NOAEL (HEC) of 465 mg/m^3. No human studies were identified that investigated the reproductive or developmental effects of

ethylbenzene following inhalation exposure. A few animal studies have investigated the reproductive and/or developmental toxicology of ethylbenzene by the inhalation route. From the study by Ungvary and Tatrai (1985), the U.S. EPA (1991) identified a LOAEL of 2,400 mg/m^3 for extra ribs in the absence of demonstrable maternal toxicity (although confidence in this particular study is low due to a number of methodological and reporting deficiencies). From the study by Andrew *et al.* (1981), the U.S. EPA (1991) identified a developmental NOAEL of 100 ppm in rabbits, which equates to a HEC NOAEL of 434 mg/m^3. From this same study, a LOAEL of 1,000 ppm (4,350 mg/m^3) was identified based on increased absolute and relative liver, kidney and spleen weights in pregnant rats, as well as minor skeletal variants in F1 offspring.

All of the short-term guideline values summarized in Table 9 are considerably lower than the apparent human irritation threshold of 100 ppm (434 mg/m^3). Therefore, all these values appear to be adequately protective of human health over their respective averaging periods. All the long-term values in Table 9 are well below the subchronic, chronic and developmental NOAEL and LOAEL values reported in the scientific literature. Thus, all the long-term air quality guideline values also appear to be adequately protective of human health.

It should be recognized that most air quality guidelines in Table 9 have the built-in assumption that all human exposure to ethylbenzene occurs *via* inhalation. They do not account for other sources, pathways and routes of ethylbenzene exposure. If exposure were apportioned to reflect these, the values presented in Table 9 would decrease in proportion to the magnitude of the exposure from these other sources, pathways and routes. However, two notable exceptions to this are the Massachusetts and Quebec jurisdictions. MDEP (1995) states that the ATCs are roughly equivalent to the U.S. EPA reference concentration (RfC), but are derived from the threshold effects exposure limit (TEL) representing 20% of an allowable exposure. The ATC thus corresponds to five times the TEL. The MAAQC for ethylbenzene in Quebec is based on the U.S. EPA RfC but is adjusted by a factor of 20% to account for the relative contribution of the sources of exposure. None of the other jurisdictions reviewed discuss exposure apportionment with respect to ethylbenzene air quality guidelines in their available documentation.

In addition, none of the agencies with air quality guidelines in Table 9 reported any special consideration of children or other sensitive individuals in air quality guideline development.

Based on the information reviewed, none of the agencies listed in Table 9 specifically acknowledged an ecological component in the development of air quality guidelines for ethylbenzene.

In addition, given the available data on the environmental fate, transport and effects of ethylbenzene, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns. The photooxidation of ethylbenzene could produce such products as peroxyacetyl nitrate, ethylphenol, benzaldehyde, acetophenone and ethylnitrobenzenes, and may contribute to the formation of photochemical smog in the atmosphere (WHO, 1996). One particular by-product of ethylbenzene photo degradation is peroxyacetyl nitrate (PAN), which is a known irritant

component of photochemical smog. However, ethylbenzene has a relatively low smog formation potential relative to alkenes, as it is less photochemically reactive (ATSDR, 1999). Yanagihara *et al.* (1977) report that its photo reactivity is intermediate to other volatile organic compounds.

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APPENDIX A

Review of Air Quality Guidelines for Ethylbenzene Used by Agencies in North America and Elsewhere

Agency: California Environmental Protection Agency (Cal EPA), Office of Environmental Health Hazard Assessment (OEHHA).
Guideline Value(s): Chronic reference exposure level (REL) = 2,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: RELs are for use in facility health risk assessments conducted for the AB 2588 Air Toxics "Hot Spots" Program.
Scientific Basis for Guideline Development: The chronic REL was developed from a NOAEL of 75 ppm for non-neoplastic lesions in rats and mice, where critical effects included nephrotoxicity, body weight reduction (rats), hyperplasia of the pituitary gland, liver cellular alterations, and necrosis (mice). The Cal EPA adjusted the NOAEL to an average experimental exposure based on the experimental exposure duration and applied an uncertainty factor of 30 to account for interspecies and intraspecies variation.
Status of Guideline (Date of Last Revision or Update): September 2002.
Additional Comments: n/a
References and Supporting Documentation: California Environmental Protection Agency (Cal EPA). 2002. Chronic Toxicity Summary for Ethylbenzene. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, September 2002. URL: http://www.oehha.org/air/chronic_rels/AllChrels.html (accessed 11 November 2003).

Agency: Government of Canada.
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Government of Canada. 1996. Health-Based Tolerable Daily Intakes/ Concentrations and Tumorigenic Doses/ Concentrations for Priority Substances. Government of Canada, Health Canada, Environmental Health Directorate, Health Protection Branch. Ottawa, ON. Government of Canada. 1999. Canadian National Ambient Air Quality Objectives (NAAQOs): Process and Status. Government of Canada, Environment Canada, Canadian Council of Ministers of the Environment (CCME). Ontario, Canada. Government of Canada. 2003. Priority Substance Lists (PSLs). Government of Canada, Environment Canada, CEPA Environmental Registry. URL: http://www.ec.gc.ca/CEPARegistry/subs_list/Priority.cfm (accessed 13 November 2003).

Agency: Louisiana Department of Environmental Quality (DEQ).
Guideline Value(s): Ambient air standard (AAS) = 10,300 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Eight-hour averaging time.
Application / How Guideline is Used by Agency: AASs are used by Louisiana DEQ to review permit applications for stationary sources that emit ethylbenzene to the atmosphere.
Scientific Basis for Guideline Development: Scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): October 2003.
Additional Comments: Louisiana DEQ classifies ethylbenzene as a suspected human carcinogen and known or suspected human reproductive toxin.
References and Supporting Documentation: Louisiana Department of Environmental Quality (DEQ). 2003. Title 33 Environmental Quality, Part III Air, Chapter 51: Comprehensive Toxic Air Pollutant Emission Control Program. Louisiana Department of Environmental Quality (DEQ). Baton, LA.

Agency:

Massachusetts Department of Environmental Protection (DEP).

Guideline Value(s):

Threshold effects exposure level (TEL) = 300 $\mu g/m^3$.
Allowable ambient limit (AAL) = 300 $\mu g/m^3$.
Allowable threshold concentration (ATC) = 1,500 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

TEL = 24-hour averaging time.
AAL = annual averaging time.
ATC = continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

The TEL and AAL guidelines are to be employed in the permitting, compliance, and enforcement of the MA DEP air quality program. The primary goal of the TEL and the AAL is designed to be protective of public health from any air contaminant causing known or potentially deleterious effects. These guidelines were developed without regard to production volume, exposure level, regulatory implication, economic considerations or control technology issues.

Scientific Basis for Guideline Development:

TELs are developed using either an occupational limit or, when a reference concentration (RfC) is published by the U.S. EPA IRIS, an RfC where appropriate and defensible. In the case of ethylbenzene, an RfC of 1.0 mg/m^3 was established by the U.S. EPA. After reviewing the basis for this RfC the MA DEP adopted a level of 1.447 mg/m^3 by dividing the NOAEL of 435 mg/m^3 that was reported for ethylbenzene in IRIS by an uncertainty factor of 300. This "calculated" RfC was then divided by five to account for exposure through media other than air based on an assumption that ambient air contributes only 20% of the total exposure. The resulting TEL was calculated as 289.4 $\mu g/m^3$ and rounded to 300 $\mu g/m^3$. The TEL is derived in such a manner considering children to be the most sensitive potential receptor.

In the case of ethylbenzene, the AAL was based on the TEL of 300 $\mu g/m^3$.

ATCs are roughly equivalent to the U.S. EPA reference concentration (RfC), but are derived from the threshold effects exposure limit (TEL) representing 20% of an allowable exposure. The ATC thus corresponds to five times the TEL. ATCs are an air concentration that would not be expected to result in adverse non-carcinogenic health effects. The ATC is derived considering acute and chronic threshold health endpoints, including reproductive effects.

Status of Guideline (Date of Last Revision or Update):

December 1995.

Additional Comments:

N/A

References and Supporting Documentation:

Massachusetts Department of Environmental Protection (DEP). 1995. Massachusetts Allowable Threshold Concentrations (ATCs). Commonwealth of Massachusetts, Executive Office of Environmental Affairs, Department of Environmental Protection. Boston, MA.

Agency:

Michigan Department of Environmental Quality (DEQ).

Guideline Value(s):

Initial threshold screening level (ITSL) = 1,000 $\mu g/m^3$.
Initial risk screening level (IRSL) = 3 $\mu g/m^3$.
Secondary risk screening level (SRSL) = 30 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

ITSL = 24-hour averaging time.
IRSL = annual averaging time.
SRSL = annual averaging time.

Application / How Guideline is Used by Agency:

Michigan air toxic rules require that each source must apply the best available control technology for toxics (T-BACT) and that the emissions of the toxic air contaminant cannot result in a maximum ambient concentration that exceeds the applicable health based screening levels (i.e., ITSL, IRSL or SRSL). ITSLs are required for any new or modified emissions source or process for which a permit to install is requested and which emits a toxic air contaminant. IRSLs apply solely to new or modified sources subject to the permit application. If an applicant cannot demonstrate compliance with the IRSL, then they may choose to demonstrate compliance with the SRSL. In this case, however, the applicant must include all sources of the toxic air contaminant emitted from the plant, not just the emission unit being permitted.

Scientific Basis for Guideline Development:

The ITSL is based on the U.S. EPA reference concentration (RfC) of 1,000 $\mu g/m^3$ for developmental effects. As the U.S. EPA does not classify ethylbenzene as a human carcinogen and, thus, has not established an inhalation cancer potency, the IRSL and SRSL are established by Michigan DEQ toxicologists based on available inhalation toxicity data and the procedures identified in Rule 229.

Status of Guideline (Date of Last Revision or Update):

ITSL = December 1990.
IRSL & SRSL = May 2002.

Additional Comments:

The Initial Threshold Screening Level (ITSL) is defined as the health based screening level for non-carcinogenic effects of a toxic air contaminant. It is determined by a number of different methods, depending upon the available toxicological data. The rules specify a hierarchy of methods for determining the ITSL. There are two health based screening levels for carcinogenic effects. These include the Initial Risk Screening Level (IRSL), which is defined as an increased cancer risk of one in one million (10^{-6}), and the Secondary Risk Screening Level (SRSL), which is defined as an increased cancer risk of one in one hundred thousand (10^{-5}). The IRSL applies only to the new or modified source subject to the permit application. If the applicant cannot demonstrate that the emissions of the toxic air contaminant meet the IRSL, they may choose to demonstrate compliance with the SRSL; however in this case they must include all sources of that toxic air contaminant emitted from the plant, not just the emission unit being permitted.

References and Supporting Documentation:

Michigan Department of Environmental Quality (DEQ). 2003. Final Screening Level List. Table 2. Michigan Department of Environmental Quality (DEQ). Air Quality Division. URL: http://www.michigan.gov/deq/0,1607,7-135-3310_4105---,00.html (accessed 12 November 2003).

Michigan Department of Environmental Quality (DEQ). 2002. Procedures for Developing Screening Levels. Michigan Department of Environmental Quality (DEQ). Air Quality Division. Lansing, Michigan.

Agency:

Minnesota Department of Health (MDH).

Guideline Value(s):

Acute health risk value (HRV) = 10,000 µg/m³.

Averaging Time to Which Guideline Applies:

Acute HRVs are comparable to a one-hour averaged concentration of chemicals or defined mixtures of chemicals in air.

Application / How Guideline is Used by Agency:

HRVs are used by the MDH and state agencies such as the Minnesota Pollution Control Agency, to assist in the assessment of potential health risks associated with chemicals in ambient air. HRVs may also be used as one set of criteria for assessing risks in the environmental review process, setting air permits, risk communication, and other site-specific assessments.

Scientific Basis for Guideline Development:

HRVs were derived using the best peer-reviewed science and public health policies available at the time of their development. Uncertainty values were incorporated to ensure that the HRVs present minimal risk to human health. The acute HRV specific to ethylbenzene was based on observed reproductive and developmental effects.

Status of Guideline (Date of Last Revision or Update):

August 2003.

Additional Comments:

The approaches used to develop HRVs are considered conservative (i.e., by design they err in the direction of protecting public health); thus, the MDH is confident that exposures to chemicals in concentrations at or below the HRV's present minimal risk to human health. In addition, because of MDH's conservative approach, exposures to chemical concentrations above HRVs do not necessarily pose a public health risk.

References and Supporting Documentation:

Minnesota Department of Health (MDH). 2003. Health Risk Values for Air. Minnesota Department of Health (MDH), Environmental Health in Minnesota. URL: http://www.health.state.mn.us/divs/eh/air/risk.pdf#search (accessed 12 November 2003).

Agency: Netherlands Research for Man and Environment (RIVM).
Guideline Value(s): Tolerable concentration in air (TCA) = 770 µg/m^3.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: Not provided.
Scientific Basis for Guideline Development: The TCA developed for ethylbenzene was derived from a NOAEL of 430 mg/m^3 for effects on the liver and kidneys in rats and mice. The NOAEL was adjusted from intermittent to continuous exposure and an uncertainty factor of 100 was applied by RIVM to account for intraspecies and interspecies variation.
Status of Guideline (Date of Last Revision or Update): March 2001.
Additional Comments: TCAs are a type of maximum permissible risk level (MPR) specific to inhalation exposure. MPRs are defined as the amount of a substance (usually a chemical substance) that any human individual can be exposed to daily during full lifetime without significant health risk.
References and Supporting Documentation: National Institute of Public Health and the Environment (RIVM). 2001. RIVM Report 711701 025 Re-evaluation of Human-Toxicological Maximum Permissible Risk Levels. URL: http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf (accessed 13 November 2003).

Agency: Newfoundland and Labrador Department of the Environment.
Guideline Value(s): One-hour air quality standard = 4,000 $\mu g/m^3$. One-hour point of impingement (POI) = 3,300 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: The minister under the Executive Council Act uses the values prescribed in the Criteria for Acceptable Air Quality for controlling air quality, where the amount of air contaminants in the atmosphere due to all sources shall not exceed these values (*i.e.*, air quality standards). Point of impingement values are used as the standard for concentrations of air contaminants from a stationary source at the point of impingement that shall not be exceeded.
Scientific Basis for Guideline Development: Scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): May 2003.
Additional Comments: n/a
References and Supporting Documentation: Newfoundland and Labrador Air Pollution Control Regulations. 2003. Newfoundland and Labrador Regulation 56/03. Government of Newfoundland and Labrador, Queen's Printer, May 2003.

Agency: New Hampshire Department of Environmental Services (DES).
Guideline Value(s): 24-hour ambient air limit (AAL) = 1,000 $\mu g/m^3$. Annual ambient air limit (AAL) = 1,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: AALs are used by the New Hampshire DES to review permit applications for sources that emit ethylbenzene to the atmosphere. Sources are regulated through a state-wide air permitting system and include any new, modified or existing stationary source, area source or device.
Scientific Basis for Guideline Development: Both the 24-hour AAL and the annual AAL were based on the reference concentration (RfC) of 1,000 $\mu g/m^3$ for developmental effects established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): March 1997.
Additional Comments: n/a
References and Supporting Documentation: New Hampshire Department of Environmental Services (DES). New Hampshire Code of Administrative Rules. Chapter Env-A 1400. Regulated Toxic Air Pollutants. New Hampshire Department of Environmental Services (DES). Concord, NH.

Agency: New Jersey Department of Environmental Protection (DEP).
Guideline Value(s): Short-term reference concentration (RfC) = 1,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: RfCs are used by the New Jersey DEP to review permit applications for sources that emit ethylbenzene to the atmosphere.
Scientific Basis for Guideline Development: The 24-hour RfC for ethylbenzene is based on the reference concentration of 1,000 $\mu g/m^3$ for developmental effects established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): April 2003.
Additional Comments: Although the U.S. EPA established the RfC for ethylbenzene on a chronic basis, the New Jersey DEP considers RfCs based on maternal, foetal or developmental effects to be of an acute (24-hour) nature.
References and Supporting Documentation: New Jersey Department of Environmental Protection (DEP). 2003. Reference Concentrations for Short-Term Inhalation Exposure. New Jersey Department of Environmental Protection (DEP), Division of Air Quality, Bureau of Air Quality Evaluation. April, 2003. New Jersey Department of Environmental Protection (DEP). 1994. Technical Manual 1003: Guidance on Preparing a Risk Assessment for Air Contaminant Emissions. New Jersey Department of Environmental Protection (DEP), Air Quality Permitting Program, Bureau of Air Quality Evaluation. Revised December 1994.

Agency: New York State Department of Environmental Conservation (NYSDEC).
Guideline Value(s): Short-term guideline concentration (SGC) = 54,000 µg/m^3. Annual guideline concentration (AGC) = 1,000 µg/m^3.
Averaging Time to Which Guideline Applies: SGC = one-hour averaging time. AGC = continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: SGCs and AGCs are used by the New York State DEC to review permit applications for sources that emit ethylbenzene to the atmosphere.
Scientific Basis for Guideline Development: The SGC was derived from the threshold limit value short-term exposure limit (TLV-STEL) of 125 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. A safety factor of 10 was applied to the STEL by the NYSDEC to account for sensitive individuals in the general population. The AGC for ethylbenzene was based on the reference concentration (RfC) of 1,000 µg/m^3 for developmental effects established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): July 2000.
Additional Comments: n/a
References and Supporting Documentation: New York State Department of Environmental Conservation (DEC). 2000. DAR – 1 AGC/SGC Tables includes TLVs & STELs for the Year 2000. New York State Department of Environmental Conservation, Division of Air Resources, Bureau of Stationary Sources. Albany, NY.

Agency: North Carolina Department of Environment and Natural Resources (ENR).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: North Carolina Department of Environment and Natural Resources (ENR). 2002. North Carolina Air Quality Rules 15A NCAC 2D (Air Pollution Control Requirements) and 15A NCAC 2Q (Air quality Permit Procedures). Section .1100 – Control of Toxic Air Pollutants. North Carolina Department of Environment and Natural Resources. Raleigh, NC.

Agency:
Ohio Environmental Protection Agency (EPA)
Guideline Value(s):
Does not exist
Averaging Time to Which Guideline Applies:
n/a
Application / How Guideline is Used by Agency:
n/a
Scientific Basis for Guideline Development:
n/a
Status of Guideline (Date of Last Revision or Update):
n/a
Additional Comments:
n/a
References and Supporting Documentation:
Ohio Environmental Protection Agency (EPA). 2002. Review of New Sources of Air Toxic Emissions Option 4. Ohio Environmental Protection Agency, Division of Air Pollution Control, Columbus, Ohio.

Agency: Oklahoma Department of Environmental Quality (DEQ)
Guideline Value(s): Maximum acceptable ambient air concentration (MAAC) = 43,427 $\mu g/m^3$
Averaging Time to Which Guideline Applies: 24-hour averaging time
Application / How Guideline is Used by Agency: MAACs are used by Oklahoma DEQ to review permit applications of sources that emit ethylbenzene to the atmosphere
Scientific Basis for Guideline Development: The 24-hour MAAC was based on the threshold limit value time weighted average (TLV-TWA) of 100 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH). A safety factor of 10 was incorporated by the Oklahoma DEQ
Status of Guideline (Date of Last Revision or Update): November 2003
Additional Comments: n/a
References and Supporting Documentation: Oklahoma Department of Environmental Quality (DEQ). 2003. Total Air Toxics Partial Listing. Oklahoma Department of Environmental Quality. URL: http://www.deq.state.ok.us/AQDnew/toxics/listings/pollutant_query_1.html (accessed 12 November 2003) Oklahoma Department of Environmental Quality (DEQ). Title 252. Department of Environmental Quality Chapter 100. Air Pollution Control. 100:252-41. Control of Emission of Hazardous and Toxic Air Contaminants. Oklahoma Department of Environmental Quality. Oklahoma City, OK.

Agency: Ontario Ministry of Environment and Energy (OMEE).
Guideline Value(s): 24-hour ambient air quality criteria (AAQC) = 1,000 $\mu g/m^3$. 10-minute ambient air quality criteria (AAQC) = 1,900 $\mu g/m^3$. Half-hour interim point of impingement (interim POI) = 3,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: AAQCs are used by OMEE to represent human health or environmental effect-based values not expected to cause adverse effects based on continuous exposure. AAQCs are not used by OMEE to permit stationary sources that emit ethylbenzene into the environment. The 30-minute POI is used by OMEE to review permit applications for stationary sources that emit ethylbenzene to the environment.
Scientific Basis for Guideline Development: OMEE adopted a reference concentration (RfC) of 1,000 $\mu g/m^3$ developed by the U.S. EPA on the basis of developmental effects as the 24-hour AAQC. OMEE based the 10-minute AAQC on the odour threshold (50% detection) of 1,900 $\mu g/m^3$ determined by an OMEE panel, which is comparable to those of the health-based exposure limits. OMEE uses a factor of three to derive half-hour POI standards and guidelines from criteria based on 24-hour averaging concentrations. This factor is derived from empirical measurements, which ensures that if the short-term limit is met, air quality standards based on long-term exposures will not be exceeded.
Status of Guideline (Date of Last Revision or Update): March 2001.
Additional Comments: The half-hour interim POI for ethylbenzene is defined as an air quality standard, pending the outcome of the Risk Management (RM) Framework for Air Standards (currently under development). The pending future effects-based POI limit for ethylbenzene is 1,400 $\mu g/m^3$.
References and Supporting Documentation: Ontario Ministry of Environment and Energy (OMEE). 2001. Summary of Point of Impingement Standards, Point of Impingement Guidelines, and Ambient Air Quality Criteria (AAQCs). Standards Development Branch, Ontario Ministry of the Environment, September 2001. Ontario Ministry of Environment and Energy (OMEE). 2001. Ontario Air Standards for Ethylbenzene. Standards Development Branch, Ontario Ministry of the Environment, March 2001.

Agency: Quebec Ministry of the Environment.
Guideline Value(s): Maximum annual air quality criteria (MAAQC) = 200 µg/m^3.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: MAAQCs are taken into account in the determination of the allowed quantity of a substance in the ambient air and in the exposure received from drinking water, food or other sources.
Scientific Basis for Guideline Development: The MAAQC for ethylbenzene was based on the reference concentration (RfC) of 1,000 µg/m^3 for developmental effects established by the U.S. EPA. The RfC was adjusted by a factor of 20% to account for the relative contribution of the sources of exposure.
Status of Guideline (Date of Last Revision or Update): May 2002.
Additional Comments: n/a
References and Supporting Documentation: Government of Quebec. 2002. Air Quality Criteria. Government of Quebec, Ministry of the Environment. URL: http://www.menv.gouv.qc.ca/air/criteres/fiches.pdf (accessed 13 November 2003).

Agency: Texas Natural Resource Conservation Commission (TNRCC).
Guideline Value(s): Short-term effects screening level (ESL) = 2,000 $\mu g/m^3$. Long-term effects screening level (ESL) = 200 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Short-term ESL = one-hour averaging time. Long-term ESL = annual averaging time.
Application / How Guideline is Used by Agency: ESLs are used to evaluate the potential for effects to occur as a result of exposure to concentrations of constituents in the air. ESLs are based on data concerning health effects, odour nuisance potential, effects with respect to vegetation, and corrosion effects. They are not ambient air standards. If predicted or measured airborne levels of a constituent do not exceed the screening level, adverse health or welfare effects would not be expected to result. If ambient levels of constituents in air exceed the screening levels, it does not necessarily indicate a problem, but rather, triggers a more in-depth review.
Scientific Basis for Guideline Development: Both the short-term and long-term ESLs for ethylbenzene were developed based on odour nuisance potential.
Status of Guideline (Date of Last Revision or Update): October 2003.
Additional Comments: n/a
References and Supporting Documentation: Texas Natural Resource Conservation Commission (TNRCC). 2003. Effects Screening Levels List. URL: http://www.tnrcc.state.tx.us/permitting/tox/esl.html (accessed 13 November 2003).

Agency: U.S. Agency for Toxic Substances and Disease Registry (ATSDR).
Guideline Value(s): Intermediate minimum risk level (MRL) = 1 ppm (4,340 $\mu g/m^3$).
Averaging Time to Which Guideline Applies: Intermediate exposure durations are based on exposure durations ranging between 14 days and 364 days.
Application / How Guideline is Used by Agency: MRLs are intended to serve as a screening tool to be used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. MRLs are not intended to define clean-up or action levels for ATSDR or other Agencies.
Scientific Basis for Guideline Development: The intermediate MRL was developed from a NOAEL of 97 ppm based on developmental effects in rats. A safety factor of 100 was applied to the study's NOAEL by the ATSDR.
Status of Guideline (Date of Last Revision or Update): July 1999.
Additional Comments: MRLs are an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects.
References and Supporting Documentation: U.S. Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Toxicological profile for ethylbenzene. URL: http://www.atsdr.cdc.gov/toxpro2.html (accessed on 11 November 2003).

Agency: U.S. Environmental Protection Agency (EPA).
Guideline Value(s): Reference Concentration (RfC) = 1,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: The RfC was developed for use by the U.S. EPA staff in risk assessments, decision-making, and regulatory activities.
Scientific Basis for Guideline Development: The RfC was developed from a NOAEL of 434 mg/m^3 based on developmental toxicity in a rat and rabbit developmental inhalation study. A safety factor of 300 was applied by the U.S. EPA to the study's NOAEL to account for unusually sensitive individuals, to adjust for interspecies conversion and to adjust for the absence of multigenerational reproductive and chronic studies.
Status of Guideline (Date of Last Revision or Update): October 2003.
Additional Comments: Ethylbenzene is not classifiable as to human carcinogenicity (classification D). The Integrated Risk Information System (IRIS) is an electronic database containing information pertaining to human health effects that may result from environmental exposure to a variety of chemicals. IRIS is prepared and maintained by the U.S. Environmental Protection Agency (EPA).
References and Supporting Documentation: U.S. Environmental Protection Agency (EPA). 2003. Integrated Risk Information System (IRIS). URL: http://www.epa.gov/iris/index.html (accessed 11 November 2003).

Agency: Vermont Agency of Natural Resources (ANR).
Guideline Value(s): Short-term hazardous ambient air standard (HAAS) = 43,500 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Eight-hour averaging time.
Application / How Guideline is Used by Agency: HAASs are used by Vermont ANR to review permit applications for stationary sources that emit ethylbenzene to the atmosphere.
Scientific Basis for Guideline Development: The eight-hour HAAS is based on the threshold limit value time weighted average (TLV-TWA) of 100 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. A safety factor of 10 was incorporated by the Vermont ANR.
Status of Guideline (Date of Last Revision or Update): November 2001.
Additional Comments: The Vermont ANR classified ethylbenzene as a non-carcinogen considered to have only short-term irritant effects.
References and Supporting Documentation: Vermont Agency of Natural Resources (ANR). 2001. Air Pollution Control Regulations, Including Amendments to the Regulations Through: November 29, 2001. Vermont Agency of Natural Resources, Air Pollution Control Division, Department of Environmental Conservation, Agency of Natural Resources. Waterbury, Vermont.

Agency: Washington Department of Ecology (DOE).
Guideline Value(s): Acceptable source impact level (ASIL) = 1,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: ASILs are used Washington DOE to review permit applications for stationary sources that emit ethylbenzene to the atmosphere.
Scientific Basis for Guideline Development: The 24-hour ASIL for ethylbenzene is based on the reference concentration (RfC) of 1,000 $\mu g/m^3$ for developmental effects established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): October 1998.
Additional Comments: n/a
References and Supporting Documentation: Washington Department of Ecology (DOE). 1998. Chapter 173-460 WAC. Controls for New Sources of Toxic Air Pollutants. Washington Department of Ecology (DOE). Olympia, WA.

Agency: World Health Organization (WHO).
Guideline Value(s): Guideline value (GV) = 22,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Annual averaging time.
Application / How Guideline is Used by Agency: The GVs were developed to provide background information which enables countries to set their national or regional air quality standards in the context of existing environmental, social, economic and cultural conditions.
Scientific Basis for Guideline Development: The GV developed for ethylbenzene was based on a NOAEL of 2,150 $\mu g/m^3$ for increased organ weight. WHO applied an uncertainty factor of 100 to the NOAEL to derive the final GV.
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: World Health Organization (WHO). 1999. Air Quality Guidelines. Chapter 3: Health-based Guidelines. World Health Organization, Geneva.